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(54) Title: PYRIMIDINE COMPOUNDS

(54) Titre: COMPOSES DE PYRIMIDINE

(57) Abstract

A pyrimidine derivative of formula (I): wherein: R1¿ is an optional substituent as defined within; Rx¿ is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula (Ib): A-B-C- as defined within; Q¿1 and Q¿2 are independently selected from aryl, a 5- or 6-membered monocyclic moiety; and a 9- or 10-membered bicyclic heterocyclic moiety; and one or both of Q¿1 and Q¿2 bears on any available carbon atom one substituent of formula (Ia) as defined within; and Q¿1 and Q¿2 are optionally further substituted; or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof; are useful as anti-cancer agents; and processes for their manufacture and pharmaceutical compositions containing them are described.

(57) Abrégé

Cette invention concerne un dérivé de la pyrimidine représenté par la formule (I) dans laquelle R1¿ est un substituant éventuel comme défini dans le descriptif; Rx¿ est pris dans halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, uréido ou carbamoyl ou dans un groupe de formule (Ib) A-B-C- comme défini dans le descriptif; Q¿1 et Q¿2 sont pris indépendamment dans aryl, une fraction monocyclique à 5 ou 6 éléments; et une fraction hétérocyclique bicyclique à 9 ou 10 éléments; et Q¿1 et Q¿2, soit l'un ou l'autre, soit les deux, porte sur n'importe quel atome de carbone un substituant de la formule (Ia) comme défini dans le descriptif: et Q¿1 et Q¿2 sont éventuellement encore substitués. L'invention concerne également un sel acceptable au plan pharmaceutique ou un ester hydrolysable in vivo de ce sel. Ces composés sont utiles comme agents anticancéreux. L'invention porte également sur des procédés de fabrication de compositions pharmaceutiques renfermant ces composés.

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Description

PYRIMIDINE COMPOUNDS

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cancer (such as anti-cell-proliferative, anti-cell migration and/or apoptotic) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments or use in the production of an anti-cancer (anti-cell-proliferation/migration and/or apoptotic) effect in a warm-blooded animal such as man.

A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

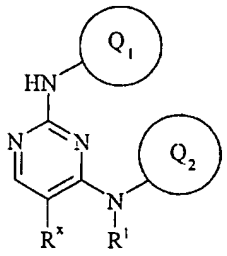
The recent convergence of oncogene and tumour suppresser gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

Furthermore, it is believed that inhibition of focal adhesion kinase (FAK), which is involved in signal transduction pathways, induces apoptosis (cell-death) and/or inhibits cell migration and an inhibitor of FAK may therefore have value as an anti-cancer agent.

The present invention is based on the discovery that certain 2,4-pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and also inhibit FAK and thus possess anti-cancer (anti-cell-migration/proliferation and/or apoptotic) properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders , psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

According to the invention there is provided a pyrimidine derivative of the formula (I):



(I)

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl [optionally substituted by one or two substituents independently selected from halo, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, hydroxy, cyano, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, carbamoyl, -$NHCOC_{1-4}$alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], *N*-phthalimido-C_{1-4}alkyl, C_{3-5}alkynyl [optionally substituted by one phenyl substituent] and C_{3-6}cycloalkyl-C_{1-6}alkyl;

wherein any phenyl or benzyl group in R^1 is optionally substituted by up to three substituents independently selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one

trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, mercapto, C_{1-3}alkylthio, carboxy, C_{1-3}alkoxycarbonyl;

R^x is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula **(Ib)**:

A-B-C-

(Ib)

wherein:

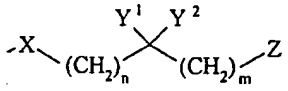
A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl, wherein said C_{1-6}alkyl, C_{3-6}alkenyl and C_{3-6}alkynyl are optionally substituted by one or more substituents selected from halo, nitro, cyano, amino, hydroxy, mercapto, carboxy, formamido, ureido, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, C_{1-3}alkoxy, trifluoromethyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl; wherein any phenyl, C_{3-8}cycloalkyl, heterocycle or heteroaryl may be optionally substituted by one or more halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, formamido, ureido, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl and C_{1-4}alkoxycarbonyl;

B is -O-, -S-, -C(O)-, -NH-, -N(C_{1-4}alkyl)-, -C(O)NH-, -C(O)N(C_{1-4}alkyl)-, -NHC(O)-, -N(C_{1-4}alkyl)C(O)- or B is a direct bond;

C is C_{1-4}alkylene or a direct bond;

Q_1 and Q_2 are independently selected from aryl, a 5- or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9- or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur);

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula **(Ia)** and Q_2 may optionally bear on any available carbon atom further substituents of the formula **(Ia)**:



(Ia)

[provided that when present in Q_1 the substituent of formula (Ia) is not adjacent to the -NH- link];

wherein:

X is $-CH_2-$, -O-, -NH-, $-NR^y-$ or -S- [wherein R^y is C_{1-4}alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C_{1-4}alkoxy or hydroxy];

Y^1 is H, C_{1-4}alkyl or as defined for Z;

Y^2 is H or C_{1-4}alkyl;

Z is R^aO-, R^bR^cN-, R^dS-, $R^eR^fNNR^g-$, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-5}cycloalkyl, and wherein said C_{1-4}alkyl and C_{2-4}alkenyl are optionally substituted by one or more phenyl ;

n is 1, 2 or 3;

m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halo, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-5}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino,

di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl;

and also independently, or where appropriate in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl, phenoxy and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, phenoxy, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear up to five substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy;

and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-6}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkoxy, cyano-C_{1-4}alkoxy, carbamoyl-C_{1-4}alkoxy, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkoxy, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkoxy, 2-aminoethoxy, 2-C_{1-4}alkylaminoethoxy, 2-di-(C_{1-4}alkyl)aminoethoxy, C_{1-4}alkoxycarbonyl-C_{1-4}alkoxy, halo-C_{1-4}alkoxy, 2-hydroxyethoxy, C_{2-4}alkanoyloxy-C_{2-4}alkoxy, 2-C_{1-4}alkoxyethoxy, carboxy-C_{1-4}alkoxy, 2-pyrrolidin-1-yl-ethoxy, 2-piperidino-ethoxy, 2-piperazin-1-yl-ethoxy, 2-morpholino-ethoxy, 2-thiomorpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{3-5}alkenyloxy, C_{3-5}alkynyloxy, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N*'-(C_{1-4}alkyl)ureido, *N*',*N*'-di-(C_{1-4}alkyl)ureido, *N*'-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N*',*N*'-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl,

N,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl,

and also independently, or where appropriate in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl, and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, phenoxy, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear one or two substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

A suitable value for "heterocycle" within the definition of A in group **(Ib)** is a fully saturated, mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, sulphur or oxygen, wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring sulphur atom may be optionally oxidised to form S-oxide(s). Suitably "heterocycle" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. "Heterocycle" may be nitrogen or carbon linked. Suitable values for "heterocycle" include morpholino, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholino, homopiperazinyl, imidazolyl, imidazolidinyl, pyrazolidinyl, dioxanyl and dioxolanyl. Preferably "heterocycle" is morpholine, piperidyl, piperazinyl, pyrrolidinyl, thiomorpholine or homopiperazinyl. More preferably "heterocycle" is morpholino.

A suitable value for "heteroaryl" within the definition of A in group **(Ib)** is a partially unsaturated or fully unsaturated, mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, sulphur or oxygen, wherein a -CH_2- group can optionally be replaced by a -C(O)-, and a ring sulphur and/or nitrogen atom may be optionally oxidised to form S-oxide(s) and/or an N-oxide. Suitably "heteroaryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. "Heteroaryl" may be nitrogen or carbon linked (but only nitrogen linked if the nitrogen link results in a neutral compound being formed). Suitable values for "heteroaryl" include thienyl, furyl, imidazolyl, thiazolyl, thiadiazolyl, pyrimidinyl, pyridinyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolyl or pyrazolyl.

Preferably "heteroaryl" is furyl, imidazolyl, thiazolyl, isoxazolyl, benzothienyl, quinolinyl, tetrazolyl and pyrazolyl. More preferably "heteroaryl" is imidazol-1-yl, fur-3-yl, isoxazol-3-yl, benzothien-6-yl, quinolin-6-yl, pyrazol-3-yl, thiazol-2-yl or tetrazol-5-yl.

A suitable value for Z in group **(Ia)** when it is a "nitrogen linked heteroaryl" is a mono or bicyclic ring that has a degree of unsaturation, containing 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring sulphur and/or nitrogen atom may be optionally oxidised to form S-oxide(s) and/or an N-oxide. Suitably "nitrogen linked heteroaryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. The nitrogen link results in a neutral compound being formed. Suitable values for "nitrogen linked heteroaryl" include imidazol-1-yl, pyrrolin-1-yl, imidazolin-1-yl, pyrazolin-1-yl, triazol-1-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, pyrrol-1-yl or pyrazol-1-yl. Preferably "nitrogen linked heteroaryl" is imidazol-1-yl.

A suitable value for Z in group **(Ia)** when it is a "nitrogen linked heterocycle" is an unsaturated mono or bicyclic ring that contains 4-12 atoms, at least one of which is selected from nitrogen, and optionally 1-3 further atoms are selected from nitrogen, sulphur or oxygen, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, and a ring sulphur may be optionally oxidised to form S-oxide(s). Suitably "nitrogen linked heterocycle" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "nitrogen linked heterocycle" include pyrrolidin-1-yl, piperidino, piperazin-1-yl, morpholino, thiomorpholino, homopiperidin-y-l or homopiperazin-1-yl. Preferably a "nitrogen linked heterocycle" is pyrrolidin-1-yl, piperazin-1-yl or morpholino.

A suitable value for Q_1 and Q_2 when it is a 5- or 6-membered monocyclic moiety containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur, or a 9- or 10-membered bicyclic heterocyclic moiety containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur; is an aromatic heterocycle, for example, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, p-isoxazine, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl or naphthyridinyl, indole, isoindazole, benzoxazole, benzimidazole,

benzothiazole, imidazo[1,5-a]pyridine, imidazo[1,2-c]pyrimidine, imidazo[1,2-a]pyrimidine, imidazo[1,5-a]pyrimidine; or a partially or fully hydrogenated derivative thereof such as for example, 1,2-dihydropyridyl, 1,2-dihydroquinolyl (all linked by a ring carbon atom), provided that an unstable aminal-type link with the amino link to the pyrimidine ring is not present.

When Q_1 is a 5- or 6-membered monocyclic moiety containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur, it will be appreciated that Q_1 is linked to the pyrimidine ring in such a way that when Q_1 bears a substituent of the formula (Ia) or (Ia') the substituent of formula (Ia) or (Ia') is not adjacent to the -NH- link. Thus, for example, 1,2,3-triazol-4-yl or 1,2,3-triazol-5-yl, are not suitable values for Q_1 when Q_1 bears a substituent of the formula (Ia) or (Ia'). It will be appreciated that there is at least one substituent of the formula (Ia) or (Ia') in each compound of formula (I), although such a substituent may be borne by Q_2 (in which case, when Q_1 bears no substituent of formula (Ia) or (Ia'), 1,2,3-triazol-4-yl or 1,2,3-triazol-5-yl, for example, are suitable values for Q_1).

When Q_1 or Q_2 is a 9- or 10-membered bicyclic heterocyclic moiety containing one or two nitrogen atoms it will be appreciated that Q_1 or Q_2 may be attached from either of the two rings of the bicyclic heterocyclic moiety.

Conveniently when Q_1 or Q_2 is a 5- or 6-membered monocyclic moiety or a 9- or 10-membered bicyclic heterocyclic moiety it is, for example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 2-quinolyl, 3-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 1-isoquinolyl, 3-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 3-cinnolyl, 6-cinnolyl, 7-cinnolyl, 2-quinazolinyl, 4-quinazolinyl, 6-quinazolinyl, 7-quinazolinyl, 2-quinoxalinyl, 5-quinoxalinyl, 6-quinoxalinyl, 1-phthalazinyl, 6-phthalazinyl, 1,5-naphthyridin-2-yl, 1,5-naphthyridin-3-yl, 1,6-naphthyridin-3-yl, 1,6-naphthyridin-7-yl, 1,7-naphthyridin-3-yl, 1,7-naphthyridin-6-yl, 1,8-naphthyridin-3-yl, 2,6-naphthyridin-6-yl or 2,7-naphthyridin-3-yl.

Particularly when Q_1 or Q_2 is a 5- or 6-membered monocyclic moiety or a 9- or 10-membered bicyclic heterocyclic moiety it is pyridyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl. More particularly 2-pyridyl, 3-pyridyl, 4-pyridyl, 1H-5-indazolyl, 5-indolyl, 6-quinolyl, 3-pyrazolyl or 2-thiazolyl.

A suitable value for Q_1 and Q_2 when it is "aryl" is a fully or partially unsaturated, mono or bicyclic carbon ring that contains 4-12 atoms. Suitably "aryl" is a monocyclic ring

containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl, naphthyl, tetralinyl or indanyl. Particularly "aryl" is phenyl, naphthyl or indanyl. More particularly "aryl" is phenyl or indanyl.

A suitable value for a ring substituent when it is a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen) is, for example, pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or p-isoxazine.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. An analogous convention applies to other generic terms.

Suitable values for the generic radicals (such as in R^1 and in substituents on Q_1 and Q_2 and also those in R^x) referred to above include those set out below:-

when it is **halo** is, for example, fluoro, chloro, bromo and iodo; **C_{2-4}alkenyl** is, for example, vinyl and allyl; **C_{2-6}alkenyl** is, for example, vinyl and allyl; when it is **C_{3-5}alkenyl** is, for example, allyl; when it is **C_{3-5}alkynyl** is, for example, propyn-2-yl; when it is **C_{2-4}alkynyl** is, for example, ethynyl and propyn-2-yl; **C_{2-6}alkynyl** is, for example, ethynyl and propyn-2-yl; when it is **C_{3-6}cycloalkyl-C_{1-6}alkyl** is, for example, cyclopropylmethyl; when it is **C_{1-5}alkanoyl** is, for example, formyl and acetyl; when it is **C_{1-4}alkoxycarbonyl** is, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and *tert*-butoxycarbonyl; when it is **C_{1-3}alkyl** is, for example, methyl, ethyl, propyl, isopropyl; when it is **C_{1-4}alkyl** is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl or *tert*-butyl; when it is **C_{1-6}alkyl** is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl or 3-methylbutyl; when it is **hydroxy-C_{1-3}alkyl** is, for example, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl and 3-hydroxypropyl; when it is **fluoro-C_{1-4}alkyl** is, for example, fluoromethyl, difluoromethyl, trifluoromethyl and 2-fluoroethyl; when it is **amino-C_{1-3}alkyl** is, for example, aminomethyl, 1-aminoethyl and 2-aminoethyl; when it is **C_{1-4}alkylamino-C_{1-3}-alkyl** is, for example, methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylamimoethyl and 3-methylaminopropyl; when it is **di-(C_{1-4}alkyl)amino-C_{1-3}alkyl** is, for example, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and

3-dimethylaminopropyl; when it is **cyano-C_{1-4}alkyl** is, for example cyanomethyl, 2-cyanoethyl and 3-cyanopropyl; when it is **C_{2-4}alkanoyloxy-C_{1-4}-alkyl** is, for example, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, 2-acetoxyethyl and 3-acetoxypropyl; when it is **C_{1-4}alkoxy-C_{1-3}alkyl** is, for example, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl; when it is **carboxy-C_{1-4}alkyl** is, for example carboxymethyl, 1-carboxyethyl, 2-carboxyethyl and 3-carboxypropyl; when it is **C_{1-4}alkoxycarbonyl-C_{1-4}alkyl** is, for example, methoxycarbonylmethyl, ethoxycarbonylmethyl, *tert*-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl; when it is **carbamoyl-C_{1-4}alkyl** is, for example carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl; when it is ***N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl** is, for example, *N*-methylcarbamoylmethyl, *N*-ethylcarbamoylmethyl, *N*-propylcarbamoylmethyl, 1-(*N*-methylcarbamoyl)ethyl, 1-(*N*-ethylcarbamoyl)ethyl, 2-(*N*-methylcarbamoyl)ethyl, 2-(*N*-ethylcarbamoyl)ethyl and 3-(*N*-methylcarbamoyl)propyl; when it is ***N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl** is, for example, *N*,*N*-dimethylcarbamoylmethyl, *N*-ethyl-*N*-methylcarbamoylmethyl, *N*,*N*-diethylcarbamoylmethyl, 1-(*N*,*N*-dimethylcarbamoyl)ethyl, 1-(*N*,*N*-diethylcarbamoyl)ethyl, 2-(*N*,*N*-dimethylcarbamoyl)ethyl, 2-(*N*,*N*-diethylcarbamoyl)ethyl and 3-(*N*,*N*-dimethylcarbamoyl)propyl; when it is **pyrrolidin-1-yl-C_{1-3}alkyl** is, for example, pyrrolidin-1-ylmethyl and 2-pyrrolidin-1-ylethyl; when it is **piperidin-1-yl-C_{1-3}alkyl** is, for example, piperidin-1-ylmethyl and 2-piperidin-1-ylethyl; when it is **piperazin-1-yl-C_{1-3}alkyl** is, for example, piperazin-1-ylmethyl and 2-piperazin-1-ylethyl; when it is **morpholino-C_{1-3}alkyl** is, for example, morpholinomethyl and 2-morpholinoethyl; when it is **thiomorpholino-C_{1-3}alkyl** is, for example, thiomorpholinomethyl and 2-thiomorpholinoethyl; when it is **imidazo-1-yl-C_{1-3}alkyl** is, for example, imidazo-1-ylmethyl and 2-imidazo-1-ylethyl; when it is **C_{1-4}alkoxy** is, for example, methoxy, ethoxy, propoxy, isopropoxy or butoxy; when it is **C_{1-3}alkoxy** is, for example, methoxy, ethoxy, propoxy or isopropoxy; when it is **cyano-C_{1-4}alkoxy** is, for example, cyanomethoxy, 1-cyanoethoxy, 2-cyanoethoxy and 3-cyanopropoxy; when it is **carbamoyl-C_{1-4}alkoxy** is, for example, carbamoylmethoxy, 1-carbamoylethoxy, 2-carbamoylethoxy and 3-carbamoylpropoxy; when

it is *N*-**C_{1-4}alkylcarbamoyl-C_{1-4}alkoxy** is, for example, *N*-methylcarbamoylmethoxy, *N*-ethylcarbamoylmethoxy, 2-(*N*-methylcarbamoyl)ethoxy, 2-(*N*-ethylcarbamoyl)ethoxy and 3-(*N*-methylcarbamoyl)propoxy; when it is ***N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkoxy** is, for example, *N*,*N*-dimethylcarbamoylmethoxy, *N*-ethyl-*N*-methylcarbamoylmethoxy, *N*,*N*-diethylcarbamoylmethoxy, 2-(*N*,*N*-dimethylcarbamoyl)ethoxy, 2-(*N*,*N*-diethylcarbamoyl)ethoxy and 3-(*N*,*N*-dimethylcarbamoyl)propoxy; when it is **2-C_{1-4}alkylaminoethoxy** is, for example, 2-(methylamino)ethoxy, 2-(ethylamino)ethoxy and 2-(propylamino)ethoxy; when it is **2-di-(C_{1-4}alkyl)aminoethoxy** is, for example, 2-(dimethylamino)ethoxy, 2-(*N*-ethyl-*N*-methylamino)ethoxy, 2-(diethylamino)ethoxy and 2-(dipropylamino)ethoxy; when it is **C_{1-4}alkoxycarbonyl-C_{1-4}alkoxy** is, for example, methoxycarbonylmethoxy, ethoxycarbonylmethoxy, 1-methoxycarbonylethoxy, 2-methoxycarbonylethoxy, 2-ethoxycarbonylethoxy and 3-methoxycarbonylpropoxy; when it is **halo-C_{1-4}alkoxy** is, for example, difluoromethoxy, trifluoromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2-bromoethoxy, 3-fluoropropoxy and 3-chloropropoxy; when it is **C_{2-4}alkanoyloxy-C_{2-4}alkoxy** is, for example, 2-acetoxyethoxy, 2-propionyloxyethoxy, 2-butyryloxyethoxy and 3-acetoxypropoxy; when it is **2-C_{1-4}alkoxyethoxy** is, for example, 2-methoxyethoxy, 2-ethoxyethoxy; when it is **carboxy-C_{1-4}alkoxy** is, for example, carboxymethoxy, 1-carboxyethoxy, 2-carboxyethoxy and 3-carboxypropoxy; when it is **C_{3-5}alkenyloxy** is, for example, allyloxy; when it is **C_{3-5}alkynyloxy** is, for example, propynyloxy; when it is **C_{1-4}alkylthio** is, for example, methylthio, ethylthio or propylthio; when it is **C_{1-4}alkylthio** is C_{1-3}alkylthio; when it is **C_{1-4}alkylsulphinyl** is, for example, methylsulphinyl, ethylsulphinyl or propylsulphinyl; when it is **C_{1-4}alkylsulphonyl** is, for example, methylsulphonyl, ethylsulphonyl or propylsulphonyl; when it is *N*-**C_{1-4}alkylcarbamoyl** is, for example *N*-methylcarbamoyl, *N*-ethylcarbamoyl and *N*-propylcarbamoyl; when it is ***N*,*N*-di-(C_{1-4}alkyl)-carbamoyl** is, for example *N*,*N*-dimethylcarbamoyl, *N*-ethyl-*N*-methylcarbamoyl and *N*,*N*-diethylcarbamoyl; when it is **C_{1-4}alkylamino** or **C_{1-3}alkylamino** is, for example, methylamino, ethylamino or propylamino; when it is **di-(C_{1-4}alkyl)amino** or **di-(C_{1-3}alkyl)amino** is, for example, dimethylamino, *N*-ethyl-*N*-methylamino, diethylamino, *N*-methyl-*N*-propylamino or dipropylamino; when it is **C_{2-4}alkanoylamino** is, for example, acetamido, propionamido or butyramido; when it is **phenyl-C_{1-4}alkyl** is, for example benzyl or 2-phenylethyl; when it is **phenyl-C_{1-4}alkoxy** is, for

example benzyloxy; when it is **-NHCOC$_{1-4}$alkyl** is, for example acetamido; when it is ***N*-phthalimido-C$_{1-4}$alkyl** is, for example 2-(*N*-phthalimido)ethyl or 3-(*N*-phthalimido)propyl; when it is **C$_{3-8}$cycloalkyl** is, for example, cyclopropyl, cyclopentyl or cyclohexyl; when it is **C$_{1-4}$alkanoyl** is, for example, acetyl or propionyl; when it is **C$_{1-4}$alkanoyloxy** is, for example, acetyloxy or propionyloxy; when it is **C$_{1-4}$alkanoylamino** is, for example, acetamido; when it is ***N*'-(C$_{1-4}$alkyl)ureido** is, for example, *N*'-methylureido or *N*'-ethylureido; when it is ***N*',*N*'-di-(C$_{1-4}$alkyl)ureido** is, for example, *N*',*N*'-dimethylureido, *N*',*N*'-diisopropylureido or *N*'-methyl-*N*'-propylureido; when it is ***N*'-(C$_{1-4}$alkyl)-*N*-(C$_{1-4}$alkyl)ureido** is, for example, *N*'-methyl-*N*-ethylureido or *N*'-methyl-*N*-methylureido; when it is ***N*',*N*'-di-(C$_{1-4}$alkyl)-*N*-(C$_{1-4}$alkyl)ureido** is, for example, *N*',*N*'-dimethyl-*N*-ethylureido, *N*'-methyl-*N*'-propyl-*N*-butylureido; when it is ***N*-(C$_{1-4}$alkyl)sulphamoyl** is, for example, *N*-methylsulphamoyl or *N*-isopropylsulphamoyl; when it is ***N*,*N*-di-(C$_{1-4}$alkyl)sulphamoyl** is, for example, *N*-methyl-*N*-ethylsulphamoyl or *N*,*N*-dipropylsulphamoyl.

A suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention is, for example, an acid-addition salt of a pyrimidine derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a pyrimidine derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C$_{1-6}$alkoxymethyl esters for example methoxymethyl, C$_{1-6}$alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters,

C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula **(I)** containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula **(I)** may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereo-isomers and geometric isomers that possess CDK and/or FAK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula **(I)** that possess CDK and/or FAK inhibitory activity.

It is also to be understood that certain compounds of the formula **(I)** can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK and/or FAK inhibitory activity.

According to a further feature of the invention there is provided a pyrimidine derivative of the formula **(I)** (as depicted above) wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl [optionally substituted by one or two substituents independently selected from halo, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, hydroxy, cyano, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, carbamoyl, -NHCOC_{1-4}alkyl, trifluoromethyl, phenylthio, phenoxy], benzyl, C_{3-5}alkenyl [optionally substituted by up to three halo

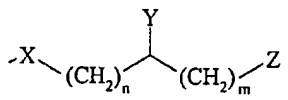
substituents, or by one trifluoromethyl substituent, or one phenyl substituent], *N*-phthalimido-C_{1-4}alkyl, C_{3-5}alkynyl and C_{3-6}cycloalkyl-C_{1-6}alkyl;

wherein any phenyl or benzyl group in R^1 is optionally substituted by up to three substituents independently selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, -SH, -S-C_{1-3}alkyl, carboxy, C_{1-3}alkoxycarbonyl;

R^3 is selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, -SH, -S-C_{1-3}alkyl, carboxy, C_{1-3}alkoxycarbonyl;

Q_1 and Q_2 are independently selected from phenyl, naphthyl, a 5- or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9- or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur); provided that when a substituent of formula **(Ia')** (defined hereinbelow) is present in Q_1 there is an available carbon atom in Q_1 such that the substituent of formula **(Ia')** is not adjacent to the -NH- link);

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula **(Ia')** and Q_2 may bear on any available carbon atom further substituents of the formula **(Ia')**



(Ia')

[provided that when present in Q_1 the substituent of formula **(Ia')** is not adjacent to the -NH- link];

wherein:

X is CH_2, O, NH or S;

Y is H or as defined for Z;

Z is OH, SH, NH_2, C_{1-4}alkoxy, C_{1-4}alkylthio, -NHC_{1-4}alkyl, -$N(C_{1-4}alkyl)_2$, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino;

n is 1, 2 or 3;

m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halo, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N,N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidin-1-yl-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, ureido (H_2N-CO-NH-), C_{1-4}alkylNH-CO-NH-, di-(C_{1-4}alkyl)N-CO-NH-, C_{1-4}alkylNH-CO-N(C_{1-4}alkyl)-, di-(C_{1-4}alkyl)N-CO-N(C_{1-4}alkyl)-, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino;

and also independently, or in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl, naphthyl, benzoyl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl and phenyl-C_{1-4}alkoxy substituents may optionally bear one or two substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy;

and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally

substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidin-1-yl-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkoxy, cyano-C_{1-4}alkoxy, carbamoyl-C_{1-4}alkoxy, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkoxy, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkoxy, 2-aminoethoxy, 2-C_{1-4}alkylaminoethoxy, 2-di-(C_{1-4}alkyl)aminoethoxy, C_{1-4}alkoxycarbonyl-C_{1-4}alkoxy, halo-C_{1-4}alkoxy, 2-hydroxyethoxy, C_{2-4}alkanoyloxy-C_{2-4}alkoxy, 2-C_{1-4}alkoxyethoxy, carboxy-C_{1-4}alkoxy, C_{3-5}alkenyloxy, C_{3-5}alkynyloxy, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, ureido (H_2N-CO-NH-), C_{1-4}alkylNH-CO-NH-, di-(C_{1-4}alkyl)N-CO-NH-, C_{1-4}alkylNH-CO-N(C_{1-4}alkyl)-, di-(C_{1-4}alkyl)N-CO-N(C_{1-4}alkyl)-, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino,

and also independently, or in addition to, the above substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl, naphthyl, benzoyl and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl and phenyl-C_{1-4}alkoxy substituents may optionally bear one or two substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Particular preferred compounds of the invention comprise a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein R^1, R^2, Q_1, Q_2, X, Y, Z, m and n have any of the meanings defined hereinbefore, or any of the following values. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter:-

(1) Q_1 and Q_2 are selected from phenyl, pyridyl, indanyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl;

(2) Q_1 and Q_2 are both phenyl or both pyridyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl or Q_1 is pyridyl and Q_2 is phenyl;

(3) Q_1 and Q_2 are both phenyl or Q_1 is 3-pyridyl and Q_2 is 2-pyridyl or Q_1 is phenyl and Q_2 is 5-indanyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1H-5-indazolyl, 5-indolyl, 6-quinolyl, 3-pyrazolyl or 2-thiazolyl or Q_1 is 3-pyridyl and Q_2 is phenyl;

(4) Q_1 and Q_2 are both phenyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl or thiazolyl;

(5) Q_1 and Q_2 are both phenyl or Q_1 is phenyl and Q_2 is pyridyl;

(6) Q_1 and Q_2 are both phenyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl or indazolyl;

(7) Q_1 and Q_2 are preferably both phenyl;

(8) Q_1 and Q_2 are selected from phenyl and pyridyl.

(9) Q_1 and Q_2 are selected from pyridyl.(10) R^1 is preferably hydrogen, benzyl, C_{3-5}alkynyl (especially propyn-2-yl), C_{3-6}cycloalkyl-C_{1-6}alkyl (especially cyclopropylmethyl), C_{1-4}alkyl [optionally substituted by one substituent selected from hydroxy, amino, halo, trifluoromethyl and cyano] or C_{3-5}alkenyl substituted by one to three halo groups;

(11) In another embodiment R^1 is hydrogen;

(12) R^1 is preferably benzyl, C_{3-5}alkynyl (especially propyn-2-yl), C_{3-6}cycloalkyl-C_{1-6}alkyl (especially cyclopropylmethyl), C_{1-4}alkyl [optionally substituted by one substituent selected from hydroxy, amino, halo, trifluoromethyl and cyano] or C_{3-5}alkenyl substituted by one halo group;

(13) R^1 is more preferably C_{3-5}alkynyl (especially propyn-2-yl) or C_{1-4}alkyl [optionally substituted by trifluoromethyl or cyano] or C_{3-5}alkenyl substituted by one bromo group;

(14) R^1 is most preferably propyn-2-yl, C_{1-4}alkyl substituted by one trifluoromethyl or one cyano group (especially cyanomethyl or 2-cyanoethyl) or C_{3-5}alkenyl substituted by one bromo group (especially $-CH_2CH=CHBr$);

(15) R^1 is most especially preferred as propyn-2-yl, cyanomethyl, 2-cyanoethyl, $-CH_2CH=CHBr$ or $-CH_2CH_2CH_2CF_3$ (especially $-CH_2CH_2CH_2CF_3$);

(16) R^1 is hydrogen, methyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH=CHBr$, $-CH_2CH=CHPh$;

(17) R^1 is hydrogen or $-CH_2CH_2CH_2CF_3$;

(18) R^x is preferably selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, -SH and -S-C_{1-3}alkyl;

(19) R^x is more preferably selected from halo (especially bromo), nitro and C_{1-3}alkyl (especially methyl);

(20) R^x is selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, -SH, -S-C_{1-3}alkyl, carboxy, C_{1-3}alkoxycarbonyl;

(21) R^x is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula **(Ib)**:

A-B-C-

(Ib)

wherein:

A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl, wherein said C_{1-6}alkyl, C_{3-6}alkenyl and C_{3-6}alkynyl are optionally substituted by one or more substituents selected from halo, nitro, mercapto, formamido, ureido, di-(C_{1-3}alkyl)amino, trifluoromethyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl; wherein any phenyl, C_{3-8}cycloalkyl, heterocycle or heteroaryl may be optionally substituted by one or more halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, formamido, ureido, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl and C_{1-4}alkoxycarbonyl;

B is -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -C(O)NH-, -C(O)N(C_{1-4}alkyl)-, -N(C_{1-4}alkyl)C(O)- or B is a direct bond;

C is C_{1-4}alkylene or a direct bond;

(22) R^x is selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, -SH, -S-C_{1-3}alkyl, carboxy;

(23) R^x is selected from halo, nitro, amino, cyano or carboxy or a group of formula **(Ib)** (as depicted above) wherein A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl, wherein said C_{1-6}alkyl and C_{3-6}alkenyl are optionally substituted by one or more substituents selected formamido, ureido, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy, phenyl, C_{3-8}cycloalkyl, or heteroaryl; wherein any phenyl, C_{3-8}cycloalkyl, heterocycle or heteroaryl may be optionally substituted by one or more halo and C_{1-4}alkyl; B is -O-, -S-, -C(O)-, -NH-, -C(O)NH- or -NHC(O)- or B is a direct bond; C is C_{1-4}alkyl or a direct bond;

(24) R^x is selected from fluoro, chloro, bromo, nitro, amino, cyano or carboxy or a group of formula **(Ib)** (as depicted above) wherein A is methyl, isopropyl, propyl, ethyl, butyl, vinyl, allyl, cyclohexyl, phenyl, morpholino, imidazolyl, isoxazolyl, quinolinyl, benzothienyl, pyrazolyl, thiazolyl, tetrazolyl or furyl, wherein said methyl, isopropyl, propyl, ethyl, butyl, vinyl, allyl, are optionally substituted by one or more substituents selected formamido, ureido, methylamine, dimethylamino, diethylamino, hydroxy, phenyl, cyclopentyl, or heteroaryl; wherein any phenyl or isoxazolyl may be optionally substituted by one or more fluoro or methyl; B is -O-, -S-, -C(O)-, -NH-, -C(O)NH- or -NHC(O)- or B is a direct bond; C is methylene or a direct bond;

(25) R^x is selected from fluoro, chloro, bromo, nitro, amino, cyano, carboxy, methyl, methoxy, ethoxy, ethoxymethyl, vinyl, allyloxymethyl, hydroxymethyl, 2-hydroxyethoxymethyl, 4-hydroxybutoxymethyl, dimethylaminomethyl, diethylaminomethyl, ureidomethyl, formamidomethyl, methylaminomethyl, isopropylaminocarbonyl, phenyl, benzyl, phenethyl, benzoylamino, 4-phenylbutyryl, 2-phenylvinyl (optionally substituted by fluoro), benzyloxymethyl, cyclohexyloxymethyl, 3-cyclopentylpropionyl, morpholino, furyl, imidazolylmethyl, isoxazolyloxymethyl (optionally substituted by methyl), quinolinylaminomethyl, benzothienylaminomethyl, pyrazolylaminomethyl, isoxazolylaminomethyl, thiazolylthiomethyl and tetrazolylthiomethyl;

(26) R^x is selected from chloro, bromo, nitro, cyano and tetrazolylthiomethyl;

(27) R^x is selected from fluoro, chloro, bromo and cyano;

(28) R^x is bromo;

(29) Preferably in the substituent of formula (Ia') X is O, Y is OH and Z is -N(C_{1-4}alkyl)$_2$; preferably n is 1 and m is 1;

(30) In the substituent of formula (Ia) X is -O-, Y^1 is OH, Y^2 is H and Z is -N(C_{1-4}alkyl)$_2$; n is 1 and m is 1;

(31) Most preferably the substituent of formula (Ia') is 3-dimethylamino-2-hydroxypropoxy;

(32) Preferably there is one substituent of formula (Ia'), and this substituent is in ring Q_1 (i.e. a ring linked via -NH-);

(33) When Q_1 is phenyl the substituent of formula (Ia') must be in either the para- or meta-position relative to the -NH-, preferably in the para-position;

(34) In the substituent of formula (Ia) X is -O-, -NH-, -NR^y- [wherein R^y is C_{1-4}alky], Y^1 is H, C_{1-4}alkyl or hydroxy, Y^2 is H or C_{1-4}alkyl, Z is R^aO-, R^bR^cN-, $R^eR^fNNR^g$-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^a, R^b, R^c, R^e, R^f and R^g are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl, and wherein said C_{1-4}alkyl are optionally substituted by one or more phenyl, n is 1 and m is 1;

(35) In the substituent of formula (Ia) X is -O-, -NH-, -NMe-, Y^1 is H, methyl or hydroxy, Y^2 is H or methyl, Z is R^aO-, R^bR^cN-, $R^eR^fNNR^g$-, imidazol-1-yl, morpholino, pyrrolidin-1-yl or piperazin-1-yl [wherein piperazin-1-yl is optionally substituted on a ring carbon or a ring nitrogen by methyl or acetyl] wherein R^a, R^b, R^c, R^e, R^f and R^g are independently selected from hydrogen, methyl, ethyl, isopropyl, isobutyl, *tert*-butyl, allyl, cyclopentyl, benzyl, n is 1 and m is 1;

(36) The substituent of formula (Ia) is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-ethoxy-2-hydroxypropoxy, 3-(*N*-isopropyl-*N*-benzylamino)-2-hydroxypropoxy,

3-(*N*-allyl-*N*-methylamino)-2-hydroxypropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-morpholinopropoxy, 3-morpholino-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-imidazol-1-ylpropoxy, 3-(*N'*,*N'*-dimethylhydrazino)-2-hydroxypropoxy, 3-*N'*,*N'*-dimethylaminopropylamino, 3-*N'*,*N'*-dimethylamino-2,2-dimethylpropylamino, 3-*N'*,*N'*-dimethylamino-2-hydroxy-*N*-methylpropylamino, 3-*N'*-isopropylaminopropylamino or 3-imidazol-1-ylpropylamino;

(37) The substituent of formula (Ia) is 3-amino-2-hydroxypropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy, 3-*N'*,*N'*-dimethylaminopropylamino, 3-*N'*-isopropylaminopropylamino or 3-imidazol-1-ylpropylamino;

(38) The substituent of formula (Ia) is 3-dimethylamino-2-hydroxypropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy or 3-imidazol-1-ylpropylamino;

(39) The substituent of formula (Ia) is 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy or 3-isopropylamino-2-hydroxypropoxy;

(40) Preferable further substituents for Q_2 include halo, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl (especially trifluoromethyl), morpholino and C_{1-4}alkyl (especially methyl);

(41) More preferable further substituents for Q_2 include halo, morpholino and C_{1-4}alkyl (especially methyl);

(42) Further substituents for Q_2 include halo, hydroxy, cyano, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, morpholino, C_{1-4}alkoxy, 2-morpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{1-4}alkylthio, carbamoyl, amino, C_{2-4}alkanoylamino, sulphamoyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl and phenoxy;

(43) Further substituents for Q_2 include fluoro, chloro, bromo, hydroxy, cyano, methyl, hydroxymethyl, hydroxyethyl, trifluoromethyl, butoxymethyl, morpholino, methoxy, butoxy,

2-morpholinoethoxy, 2-imidazo-1-ylethoxy, methylthio, carbamoyl, amino, acetylamino, sulphamoyl, benzyl, benzyloxy, phenyl and phenoxy;

(44) A further substituent for Q_2 is methyl;

(45) Q_2 is unsubstituted or substituted by methyl;

(46) Further substituents for Q_2 include fluoro, chloro, bromo, cyano, methyl, hydroxymethyl, methoxy;

(47) Further substituents for Q_2 include fluoro, bromo, methyl, hydroxymethyl, methoxy, 2-imidazo-1-ylethoxy and phenyl;

(48) A further substituent for Q_2 is chloro.

(49) Q_2 is unsubstituted or substituted by chloro;

(50) Preferably the ring Q_1 or Q_2 not bearing the substituent of formula **(Ia')** is substituted by one or two further substituents, preferably halo, morpholino and/or C_{1-4}alkyl (especially methyl);

(51) Most preferably the ring Q_1 bears the substituent of formula **(Ia')** and Q_2 is substituted by one or two further substituents, selected preferably from halo, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl (especially trifluoromethyl), morpholino and C_{1-4}alkyl (especially methyl);

(52) A further substituent for Q_1 is halo;

(53) A further substituent for Q_1 is fluoro;

(54) Q_1 is unsubstituted except for a substituent of formula **(Ia)** or **(Ia')**.

A preferred compound of the invention is a pyrimidine derivative of the formula **(I)**, or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein:

Q_1 and Q_2 are both phenyl;

R^x is bromo, nitro or methyl (especially bromo or nitro);

R^1 is C_{1-4}alkyl substituted by one cyano group (especially cyanomethyl);

or alternatively R^1 $-CH_2CH=CHBr$ or $-CH_2CH_2CH_2CF_3$ (especially $-CH_2CH_2CH_2CF_3$);

Q_1 bears one substituent of formula **(Ia')** (especially 3-dimethylamino-2-hydroxypropoxy), preferably in the para-position; and

Q_2 bears one or two substituents independently selected from halo, morpholino and C_{1-4}alkyl (especially methyl).

In one aspect of the invention, a preferred compound of the invention is a pyrimidine derivative of the formula **(I)**, or pharmaceutically acceptable salt or *in vivo* hydrolysable ester

thereof, wherein:

Q_1 and Q_2 are both phenyl or both pyridyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl or Q_1 is pyridyl and Q_2 is phenyl;

R^1 is hydrogen, methyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH=CHBr$ or $-CH_2CH=CHPh$;

R^x is fluoro, chloro, bromo, nitro, amino, cyano, carboxy, methyl, methoxy, ethoxy, ethoxymethyl, vinyl, allyloxymethyl, hydroxymethyl, 2-hydroxyethoxymethyl, 4-hydroxybutoxymethyl, dimethylaminomethyl, diethylaminomethyl, ureidomethyl, formamidomethyl, methylaminomethyl, isopropylaminocarbonyl, phenyl, benzyl, phenethyl, benzoylamino, 4-phenylbutyryl, 2-phenylvinyl (optionally substituted by fluoro), benzyloxymethyl, cyclohexyloxymethyl, 3-cyclopentylpropionyl, morpholino, furyl, imidazolylmethyl, isoxazolyloxymethyl (optionally substituted by methyl), quinolinylaminomethyl, benzothienylaminomethyl, pyrazolylaminomethyl, isoxazolylaminomethyl, thiazolylthiomethyl or tetrazolylthiomethyl;

Q_1 is optionally substituted by fluoro and is substituted by a group of formula **(Ia)** which is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy, 3-ethoxy-2-hydroxypropoxy, 3-(*N*-isopropyl-*N*-benzylamino)-2-hydroxypropoxy, 3-(*N*-allyl-*N*-methylamino)-2-hydroxypropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-morpholinopropoxy, 3-morpholino-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-imidazol-1-ylpropoxy, 3-(*N'*,*N'*-dimethylhydrazino)-2-hydroxypropoxy, 3-*N'*,*N'*-dimethylaminopropylamino, 3-*N'*,*N'*-dimethylamino-2,2-dimethylpropylamino, 3-*N'*,*N'*-dimethylamino-2-hydroxy-*N*-methylpropylamino, 3-*N'*-isopropylaminopropylamino or 3-imidazol-1-ylpropylamino; and

Q_2 is optionally substituted by one or two halo, hydroxy, cyano, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, morpholino, C_{1-4}alkoxy,

2-morpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{1-4}alkylthio, carbamoyl, amino, C_{2-4}alkanoylamino, sulphamoyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl and phenoxy.

In another aspect of the invention, a preferred compound of the invention is a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein:

Q_1 and Q_2 are both phenyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl or thiazolyl;

R^1 is hydrogen;

R^x is selected from chloro, bromo, nitro, cyano and tetrazolylthiomethyl;

Q_1 is substituted by a group of formula (Ia) which is 3-dimethylamino-2-hydroxypropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy or 3-imidazol-1-ylpropylamino; and

Q_2 is optionally substituted by one or two fluoro, bromo, methyl, hydroxymethyl, methoxy, 2-imidazo-1-ylethoxy and phenyl.

In another aspect of the invention, a preferred compound of the invention is a pyrimidine derivative of the formula (I), or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, wherein:

Q_1 and Q_2 are both phenyl or Q_1 is phenyl and Q_2 is indanyl, pyridyl or indazolyl;

R^1 is hydrogen or $-CH_2CH_2CH_2CF_3$;

R^x is selected from fluoro, chloro, bromo and cyano;

Q_1 is substituted by a group of formula (Ia) which is 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy or 3-isopropylamino-2-hydroxypropoxy; and

Q_2 is optionally substituted by one or two fluoro, bromo, methyl, hydroxymethyl, methoxy, 2-imidazo-1-ylethoxy and phenyl.

A specific preferred compound of the invention is the following pyrimidine derivative of the formula (I):-

2-{4-[3-(*N*,*N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(4-bromoanilino)-5-bromo-pyrimidine;

2-{4-[3-(*N*,*N*-Dimethyl)amino-2-hydroxy-propoxy]anilino}-4-(2-fluoro-5-methylanilino)-5-bromo-pyrimidine;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In one aspect of the invention preferred compounds of the invention are those of Examples 3, 118, 151, 188, 218, 234 or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

In another aspect of the invention preferred compounds of the invention are those of Examples 47 or 111 or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

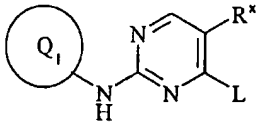
In a further aspect of the invention preferred compounds of the invention include any one of the Examples or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound or a pharmaceutically acceptable salt thereof.

A pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Such processes, when used to prepare a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, are provided as a further feature of the invention and are illustrated by the following representative examples in which, unless otherwise stated R^1, Q_1, Q_2, R^x, X, Y^1, Y^2, Z_1 m and n have any of the meanings defined hereinbefore for a pyrimidine derivative of the formula (I) and unless another substituent is drawn on ring Q_1 or Q_2 the ring may bear any of the substituents described hereinbefore (optionally protected as necessary). Where a substituent is drawn on ring Q_1, this includes (unless stated otherwise) the possibilities of the substituent being on ring Q_2 in addition to, or instead of the substituent being on ring Q_1. Where X is defined in this section as -NH- it is to be understood that this also includes the posibility of X as $-NR^y-$. Necessary starting materials may be obtained by standard procedures of organic chemistry (see for example, Advanced Organic Chemistry (Wiley-Interscience), Jerry March - also useful for general guidance on reaction conditions and reagents). The preparation of such starting materials is described within the accompanying non-limiting processes and Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

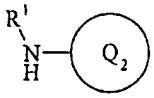
Thus, as a further feature of the invention there are provided the following processes which comprises of:-

a) reacting a pyrimidine of formula (II):



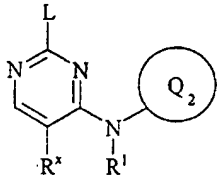
(II)

wherein L is a displaceable group as defined below, with a compound of formula (III):



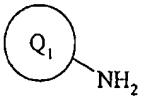
(III)

b) reaction of a pyrimidine of formula (IV):



(IV)

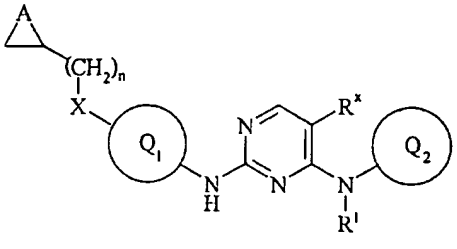
wherein L is a displaceable group as defined below, with a compound of formula (V):



(V)

c) for compounds of formula (I) where n is 1, 2 or 3, m = 1, Y^2 is H and Y^1 is OH, NH_2 or SH by

reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

wherein A is O, S or NH; with a nucleophile of formula **(VII)**:

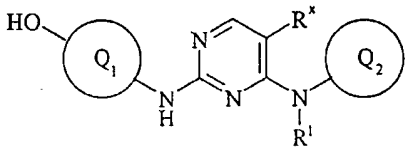
Z-D

(VII)

wherein D is H or a suitable counter-ion;

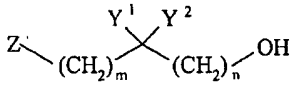
d) for compounds of formula **(I)** where X is oxygen:

by reaction of an alcohol of formula **(VIII)**:



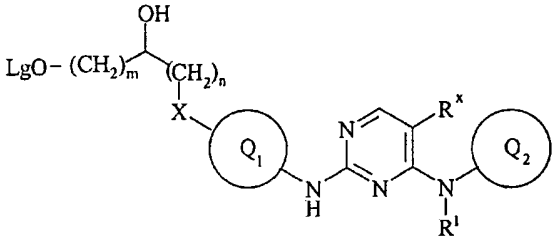
(VIII)

with an alcohol of formula **(IX)**:



(IX)

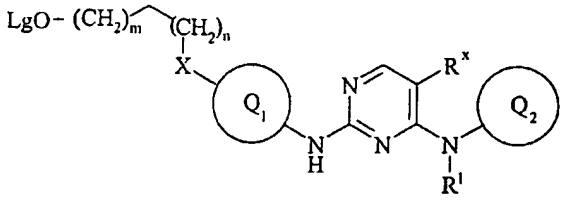
e) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula **(X)**:



(X)

wherein LgO is a leaving group as defined below; with a nucleophile of formula **(VII)**;

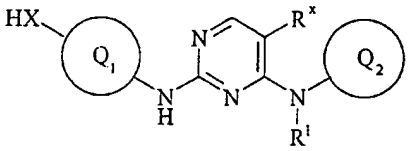
f) for compounds of formula **(I)** wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula **(XI)**:



(XI)

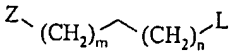
wherein LgO is a leaving group as defined below; with a nucleophile of formula (VII);

g) for compounds of formula (I) wherein X is -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XII):



(XII)

with a compound of formula (XIII)



(XIII)

wherein L is a displaceable group as defined below;

h) for compounds of formula (I) in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halo or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group. Alternative suitable groups for L include halo, mesyl, methylthio and methylsulphinyl.

D is hydrogen or a counter-ion. When D is a counter-ion, suitable values for D include sodium and potassium.

LgO is a leaving group. Suitable values for LgO include mesylate and tosylate.

Specific reaction conditions for the above reactions are as follows:-

Process a)

Pyrimidines of formula **(II)** and anilines of formula **(III)** may be reacted together:

i) optionally in the presence of a suitable acid, for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid. The reaction is preferably carried out in a suitable inert solvent or diluent, for example dichloromethane (DCM), acetonitrile, butanol, tetramethylene sulphone, tetrahydrofuran, 1,2-dimethoxyethane, *N,N*-dimethylformamide, *N,N*-dimethylacetamide or *N*-methylpyrrolidin-2-one, and at a temperature in the range, for example, 0°to 150°C, conveniently at or near reflux temperature; or

ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-t-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula **(II)** may be prepared according to the following scheme:

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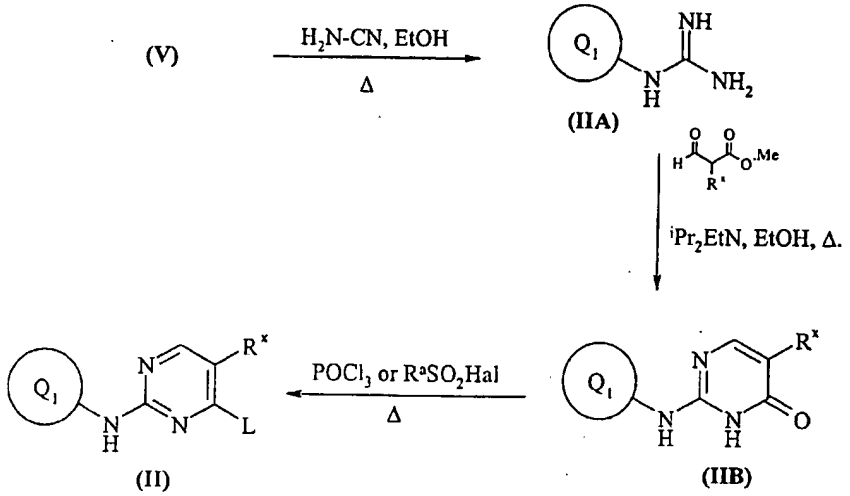


wherein R^a is an optionally substituted alkyl or aryl group and L is a displaceable group as defined above. Preferably R^a is methyl, ethyl or p-tolyl.

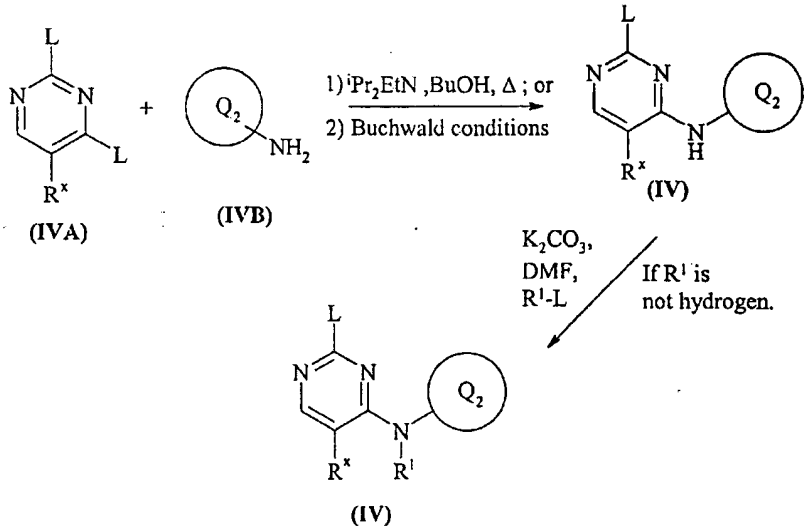
Anilines of formula (III) are commercially available or are prepared by processes known in the art.

Process b)

Pyrimidines of formula (IV) and anilines of formula (V) may be reacted together, i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid such as those defined above (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or

ii) under standard Buchwald conditions as described above.

Pyrimidines of formula (IV) are prepared according to the following scheme:



wherein L is a displaceable group as defined above and R^1 is not hydrogen.

The anilines of formula (V) are commercially available or are prepared by processes known in the art.

Pyrimidines of the formula (IVA) are commercially available or may be prepared by, for example, reacting a compound of formula (IVA) in which L is -OH (i.e. a uracil), with $POCl_3$ to give a compound of formula (IVA) in which L is -Cl.

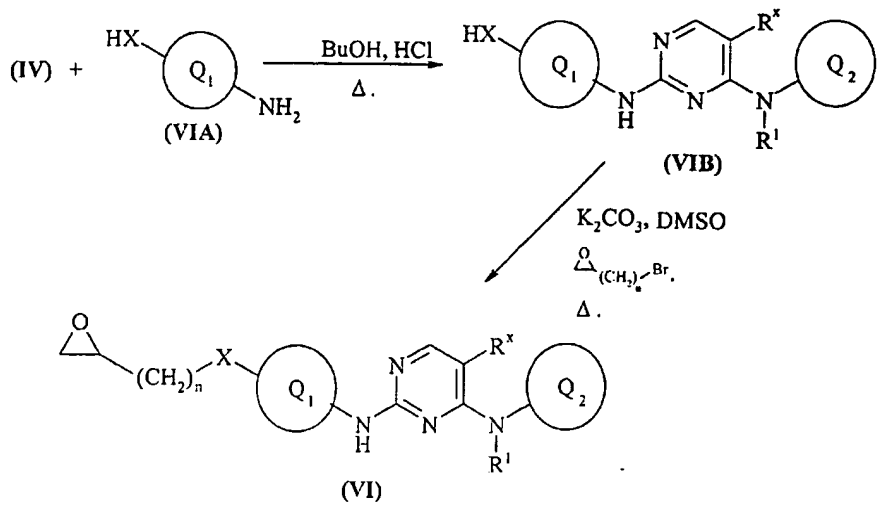
Process c)

Three membered heteroalkyl rings of formula (VI) and nucleophiles of formula (VII) are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example *N,N*-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran.

Compounds formula (VI) may be prepared according to the following schemes:

Scheme I):

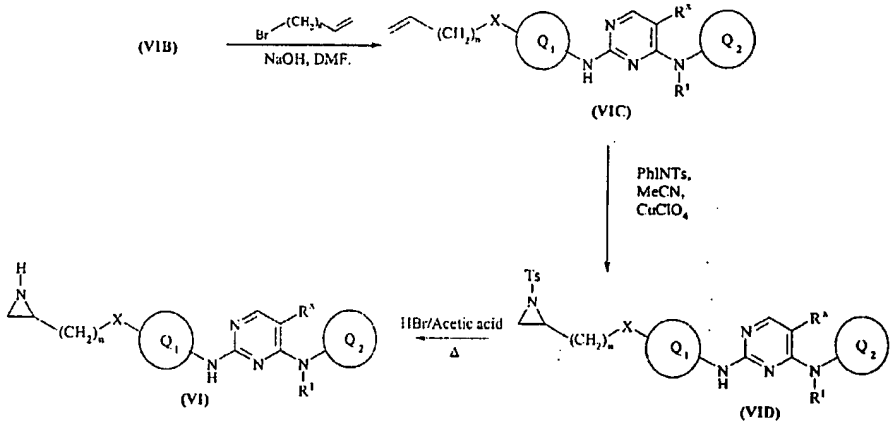
For compounds of formula (VI) where A is O, and X is not carbon:



The conversion of (VIB) to (VI) may also be achieved by reaction with $Br-(CH_2)_n-CHO$, or an equivalent ester, in DMF and the presence of a base, followed by reaction with a sulphur ylide such as (Me_2SOCH_2) in an inert solvent such as THF (see scheme V).

Scheme II):

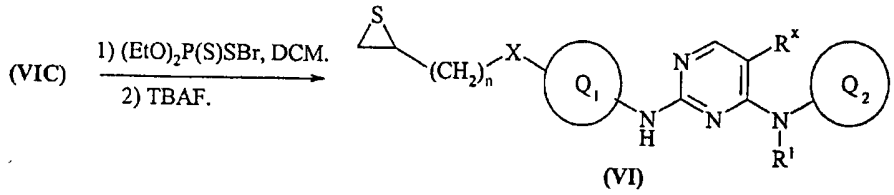
For compounds of formula (VI) where A is NH, and X is not carbon:



(for PhINTs see, for example, Tet. Let., 1997, 38 (39), 6897-6900; compounds of formula (VIC) may also be oxidised to the epoxide using conditions similar to that in Scheme IV) below);

Scheme III):

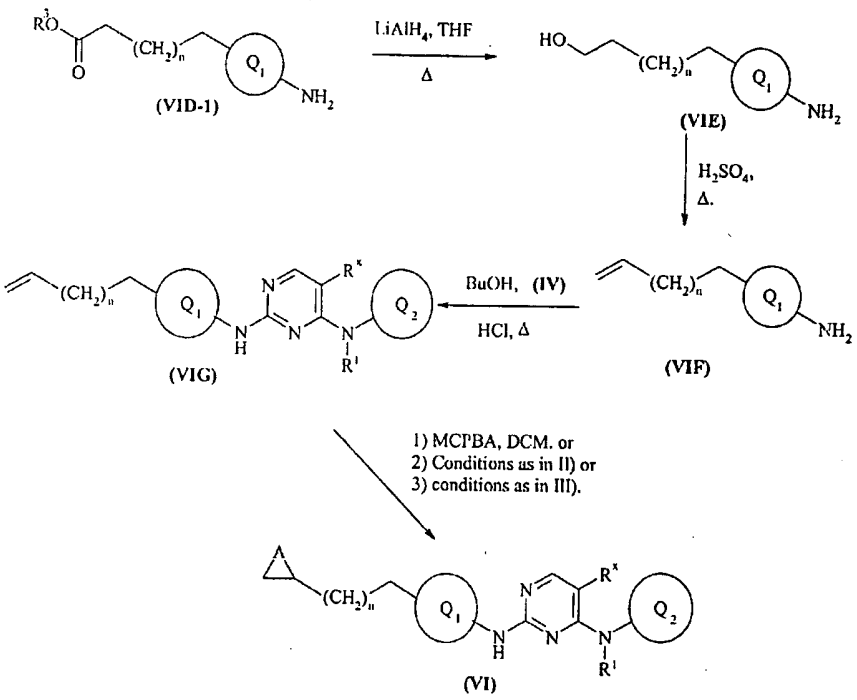
For compounds of formula (VI) where A is S, and X is not carbon:



(for example see *Synlett*, 1994, 267-268);

Scheme IV):

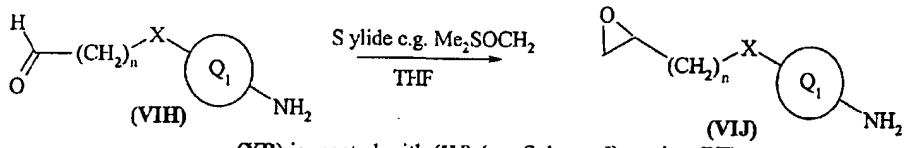
For compounds of formula (VI) where X is carbon



wherein R^3 together with the -COO- group to which it is attached forms an ester moiety, for example a methyl ester or an ethyl ester.

Scheme V)

For compounds of formula (VI) wherein X is CH_2, O, NH or S; Y is OH; n is 1, 2 or 3 and m is 1 :



(XB) is reacted with (IV) (see Scheme I) to give (VI).

An equivalent ester of (VIH) may also be used. See also Russ. Chem. Rev. 47, 975-990, 1978.

Compounds of formula (VIH), (VII), (VIA) and (VID-1) are commercially available or are prepared by processes known in the art.

Process d)

Alcohols (e.g. phenols) of formula (VIII) and alcohols of formula (IX) can be reacted together under standard Mitsunobu conditions. For example in the presence of diethyl azodicarboxylate and triphenyl phosphine, in a suitable solvent such as dichloromethane, toluene or tetrahydrofuran, and at a temperature in the range of 0 to 80°C, preferably in the range of 20 to 60°C. Alternatively, alcohols (phenols) of formula (VIII) may be alkylated with a suitable compound of formula (IX) in which the terminal hydroxy group has been replaced by a suitable leaving group.

Alcohols of formula (VIII) are made according to the process in I) above for the synthesis of intermediate (VIB) (where X is oxygen).

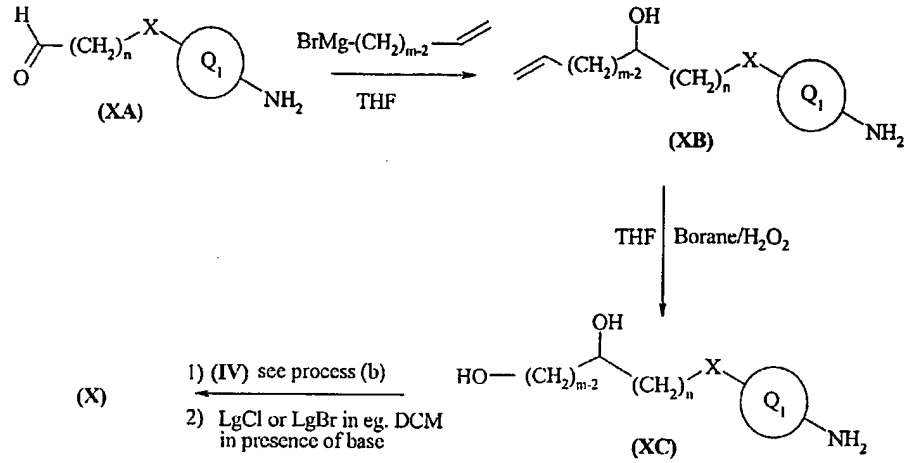
Alcohols of formula (IX) are commercially available or are made by processes known in the art.

In a process analogous to process d), compounds in which X is -S- may be prepared by reaction of a compound of formula (VIII) in which the hydroxy group is -SH, with a compound of formula (IX) in which the hydroxy group is a leaving group such as mesylate or tosylate.

Process e)

Compounds of formula (X) wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 is OH, Y^2 is H and m is 2 or 3 and nucleophiles of formula (VII) are reacted together at a temperature in the range of 20° to 100°C, preferably 20° to 50°C, optionally in the presence of a suitable solvent, for example *N,N*-dimethylformamide, dimethyl sulphoxide or tetrahydrofuran, and optionally in the presence of a suitable base, such as potassium carbonate.

Compounds of formula (X) are prepared according to the following scheme (m is 2 or 3):



The order of steps 1) and 2) in the final step may be reversed. A suitable base for step 2) is triethylamine.

Compounds of formula (XA) and (VII) are commercially available or are prepared by processes known in the art. For example, compounds of formula (XA) in which X is -NH-, -O- or -S- may be prepared by reaction of a compound of formula (VIA) with a suitable haloaldehyde or equivalent ester under standard conditions for such reactions.

Process f)

Compounds of formula (XI) and nucleophiles of formula (VII) are reacted together as described for process e) above.

Compounds of formula (XI) are prepared in an analogous manner to step 2) in the final step of the process for preparing compounds of formula (X) above. The necessary primary alcohol starting materials are commercially available or are prepared by processes known in the art.

Process g)

Compounds of formula (XII) and (XIII) are reacted in an inert solvent such as DMF in the presence of a base such as potassium carbonate.

Compounds of formula (XII) are of the same generic formula as compounds of formula (VIB) described herein and are prepared as described for those compounds (see

Scheme I). Compounds of formula (XIII) are commercially available or are prepared by processes known in the art.

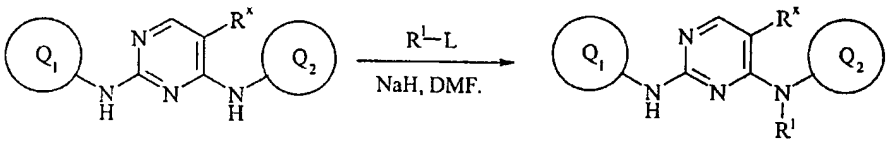
Process h)

For the compounds of formula (I) in which Z is SH, the conversion of a thioacetate group in a corresponding compound is carried out as described herein for the conversion of compounds of formula (IJ) into (IK).

Suitable starting materials containing a thioacetate group are prepared from corresponding compounds containing a leaving group such as mesylate or tosylate (prepared using standard conditions from the corresponding hydroxy compound) using thiol acetic acid as described herein for the conversion of compounds of formula (IG) into (IJ).

Examples of conversions of a compound of formula (I) into another compound of formula (I) are:

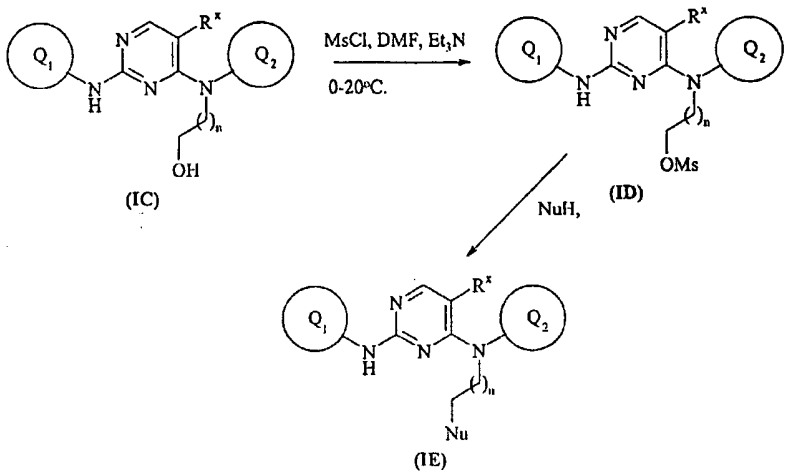
i) conversion of R^1 as hydrogen into other R^1 for example:



(IA) (IB)

wherein L is a displaceable group as defined above and R^1 in the above diagram is not equal to hydrogen;

ii) conversion of R^1 as a substituted side chain into another substituted side chain, for example:

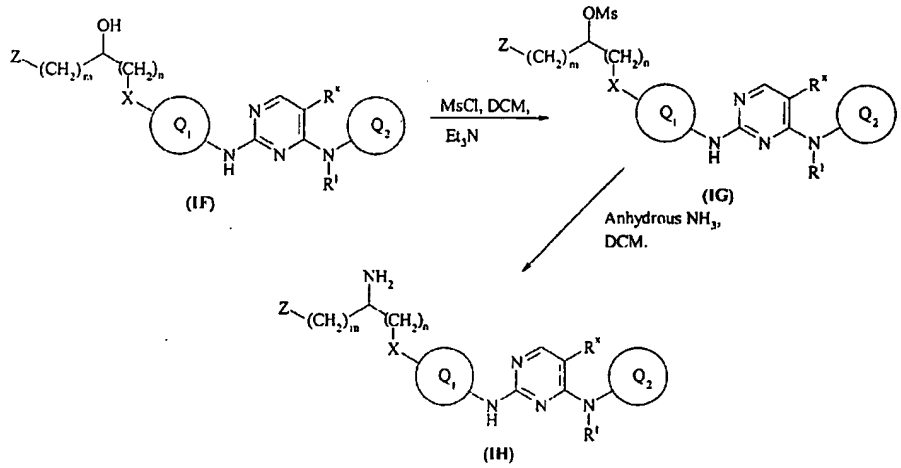


(IC) (ID) (IE)

wherein Ms is methanesulphonyl, and Nu is a nucleophile that introduces a substituent that is an optional substituent for R^1 as defined in formula (I), such as Nu is $-NH_2$, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$ or -CN (NB the hydroxyl moiety does not necessarily have to be on the terminal carbon as depicted above);

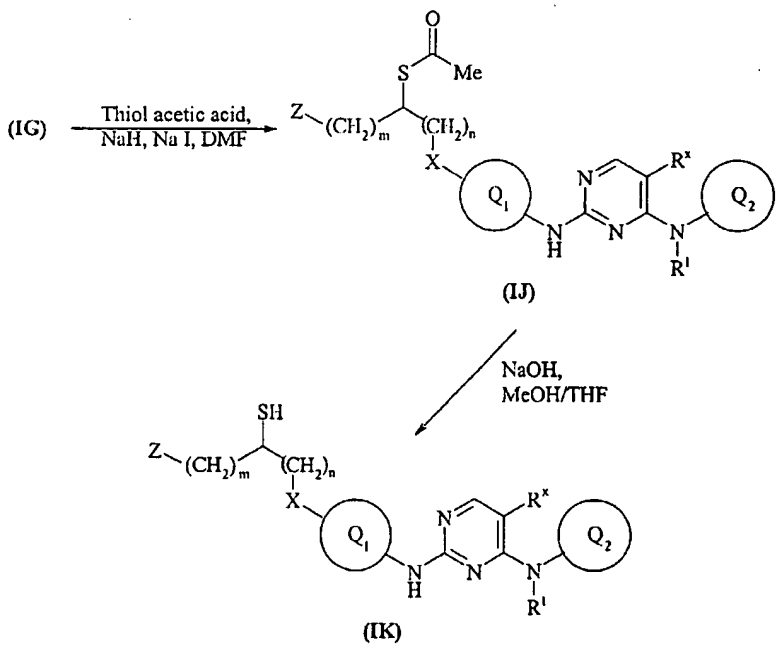
iii) conversion of one side chain of formula **(Ia)** into another side chain of formula **(Ia)**, for example:

I) for compounds of formula (I) where Y^2 is H and Y^1 is NH_2 (depicted below using ammonia), C_{1-4}alkoxy, C_{1-4}alkylthio, $-NHC_{1-4}$alkyl, $-N(C_{1-4}alkyl)_2$, $-NHC_{3-8}$cycloalkyl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholino or thiomorpholino;

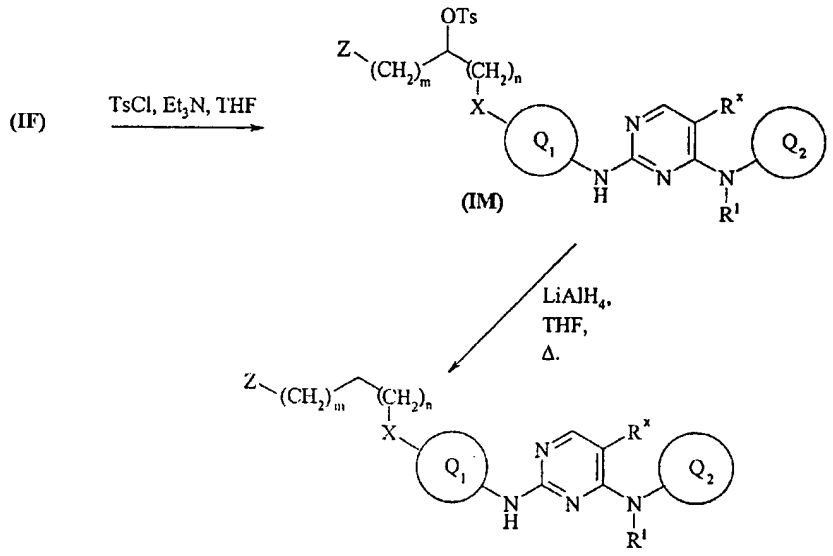


or:

II) for compounds of formula (I) where Y^2 is H and Y^1 is S:



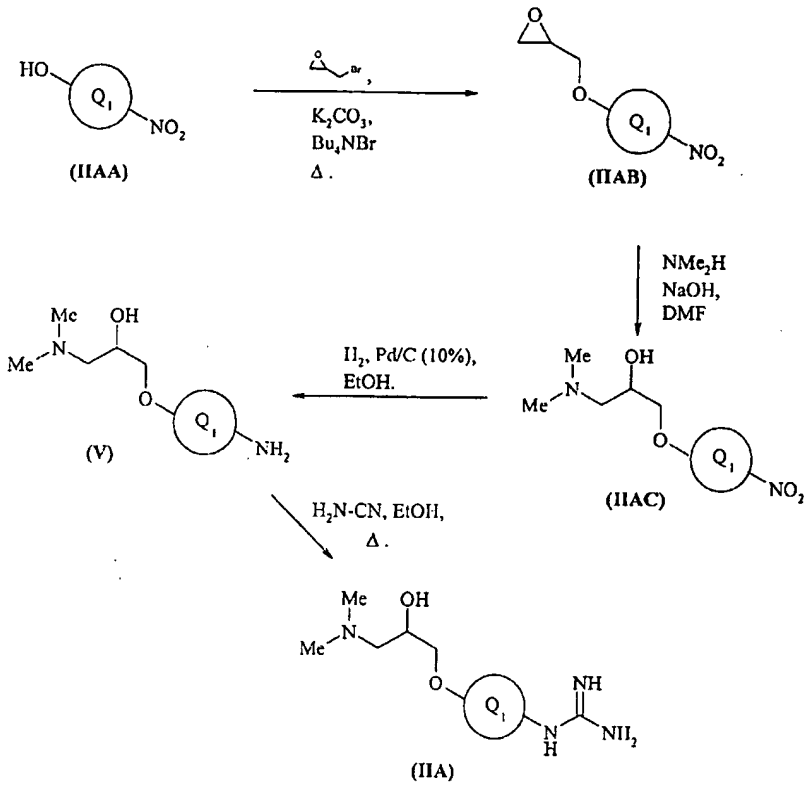
III) for compounds of formula (I) where Y^2 is H and Y^1 is H:



It will be appreciated that these reactions are also suitable for conversion of one side chain of formula **(Ia')** into another side chain of formula **(Ia')**.

iv) conversion of one value of R^x into another value of R^x, using standard techniques, for example, conversion of R^x as hydroxy into C_{1-3}alkoxy.

The skilled reader will appreciate that the manipulation of the side chain **(Ia)** or **(Ia')** described in Processes c), d), e), f), g) and h) and and iii) above and of the sidechain R^1 in i) and ii) above may also be performed on intermediates for example to make intermediates of formula **(II)**, **(IIA)**, **(IIB)**, or **(V)**. For example:



A preferred process of the invention is Process b).

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts

conditions; and the introduction of a halo group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with

a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Many of the intermediates defined herein are novel, for example, those of the formula II and IV and these are provided as a further feature of the invention.

ASSAYS

As stated hereinbefore the pyrimidine derivative defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK and/or FAK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

CDK4 Inhibition Assay

The following abbreviations have been used :-

HEPES is *N*-(2-Hydroxyethyl)piperazine-*N'*-(2-ethanesulfonic acid)

DTT is Dithiothretiol

PMSF is Phenylmethylsulfonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma). In each well was placed the compound to be tested (diluted in DMSO and water to correct concentrations) and in control wells either p16 as an inhibitor control or DMSO as a positive control.

Approximately 0.5µl of CDK4/Cyclin D1 partially-purified enzyme (amount dependent on enzyme activity) diluted in 25µl incubation buffer was added to each well then 20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and

0.14μCi [γ-33-P]-Adenosine Triphosphate), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150μL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100μM Sodium vanadate, 100μM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

As a control, another known inhibitor of CDK4 may be used in place of p16.

Test substrate

In this assay only part of the retinoblastoma (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEX 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column (Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl2, 1mM DTT, imM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed

overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK4 and Cyclin D1

CDK4 and Cyclin D1 were cloned from RNA from MCF-7 cell line (obtained from ATCC number:HTB22, breast adenocarcinoma line) as follows. The RNA was prepared from MCF-7 cells, then reverse transcribed using oligo dT primers. PCR was used to amplify the complete coding sequence of each gene [CDK4 amino acids 1-303; Ref. Cell 1992 Oct 16; 71(2): 323-334; Matsushime H., Ewen M.E., Stron D.K., Kato J.Y., Hanks S.K., Roussel M.F., Sherr C.J. and Cyclin D1 amino acids 1-296; Ref. Cold Spring Harb. Symp. Quant. Biol., 1991; 56:93-97; Arnold A., Motokura T., Bloom T., Kroncnburg, Ruderman J., Juppner H., Kim H.G.].

After sequencing the PCR products were cloned using standard techniques into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number : V1392-20). The PCR products were then dually expressed [using a standard virus Baculogold co-infection technique] into the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm -Commercially available).

The following Example provides details of the production of Cyclin D1/CDK4 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin D1 & CDK4.

Example production of Cyclin D1/CDK4

SF21 cells grown in a roller bottle culture to 2.33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86 x 10E6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

10 x 500ml were infected with JS303 Cyclin D1 virus titre - 9 x 10E7 pfu/ml. JS304 CDK4 virus titre - 1 x 10E8 pfu/ml.

Cyclin D1 $\frac{1.86 \times 10E6 \times 500 \times 3}{0.9 \times 10^8}$ = 31 ml of virus for each 500 ml. bottle.

CDK4 $\frac{1.86 \times 10E6 \times 500 \times 3}{}$ = 28 ml of virus for each 500 ml. bottle.

1×10^8

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 3 days (72 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58 x 10E6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 mls. lots. The supernatant was discarded.

20 pellets of ~ 4 x 10E8 cells/pellet were snap frozen in LN_2 and stored at -80°C in CCRF cold room. The SF21 cells were then hypotonically lysed by resuspending in lysis buffer (50mM HEPES pH 7.5, 10mM magnesium chloride, 1mM DTT, 10mM glycerophosphate, 0.1mM PMSF, 0.1mM sodium fluoride, 0.1mM sodium orthovanadate, 5ug/ml aprotinin, 5ug/ml leupeptin and 20% w/v sucrose), and adding ice cold deionised water. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK4 and Cyclin D1 were coeluted with 375mM NaCl in lysis buffer, and their presence checked by western blot, using suitable anti-CDK4 and anti-Cyclin D1 antibodies (obtained from Santa Cruz Biotechnology, California, US).

p16 control (Nature 366.:704-707; 1993; Serrano M, Hannon GJ, Beach D)

p16 (the natural inhibitor of CDK4/Cyclin D1) was amplified from HeLa cDNA (Hela cells obtained from ATCC CCL2, human epitheloid carcinoma from cervix; Cancer Res. 12: 264, 1952), cloned into pTB 375 NBSE which had a 5' His tag, and transformed using standard techniques into BL21 (DE3) pLysS cells (obtained from Promega; Ref. Studier F.W. and Moffat B.A., J. Mol. Biol., 189, 113, 1986). A 1 litre culture was grown to the appropriate OD then induced with IPTG to express p16 overnight. The cells were then lysed by sonication in 50mM sodium phosphate, 0.5M sodium chloride, PMSF, 0.5µg/ml leupeptin and 0.5µg/ml aprotinin. The mixture was spun down, the supernatant added to nickel chelate beads and mixed for 1 ½ hours. The beads were washed in sodium phosphate, NaCl pH 6.0 and p16 product eluted in sodium phosphate, NaCl pH 7.4 with 200mM imidazole.

The pTB NBSE was constructed from pTB 375 NBPE as follows :-

p TB375

The background vector used for generation of pTB 375 was pZEN0042 (see UK patent 2253852) and contained the tetA/tetR inducble tetracycline resistance sequence from plasmid

RP4 and the cer stability sequence from plasmid pKS492 in a pAT153 derived background. pTB375 was generated by the addition of an expression cassette consisting of the T7 gene 10 promoter, multiple cloning site and T7 gene 10 termination sequence. In addition, a terminator sequence designed to reduce transcriptional readthrough from the background vector was included upstream of the expression cassette.

pTB 375 NBPE

The unique EcoRI restriction site present in pTB 375 was removed. A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, PstI and EcoRI was introduced into pTB 375 between the NdeI and BamHI sites destroying the original BamHI site present in pTB 375.

pTB 375 NBSE

A new multiple cloning site containing the recognition sequences for the restriction enzymes NdeI, BamHI, SmaI and EcoRI was introduced into pTB 375 NBPE between the NdeI and EcoRI sites. The oligonucleotide containing these restriction sites also contained 6 histidine codons located between the NdeI and BamHI sites in the same reading frame as the inititiator codon (ATG) present within the NdeI site.

By analogy to the above, assays designed to assess inhibition of CDK2 and CDK6 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

If using CDK2 with Cyclin E partial co-purification may be achieved as follows:- Sf21 cells are resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF, 1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser. After centrifugation, the supernatant is loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). CDK2 and Cyclin E are coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution is checked by western blot using both anti-CDK2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

FAK3 Kinase Inhibition Assay

This assay determines the ability of a test compound to inhibit tyrosine kinase activity of human Focal Adhesion Kinase (FAK).

DNA encoding FAK is obtained by total gene synthesis (Edwards M, International Biotechnology Lab 5(3), 19-25, 1987) or by cloning. These are then expressed in a suitable expression system to obtain polypeptide with tyrosine kinase activity. For example, FAK, obtained by expression of recombinant protein in insect cells, was found to display intrinsic tyrosine kinase activity.

FAK (full length human cDNA described by Andre et al (Biochemical and Biophysical Research Communications, 1993, 190 (1): 140-147; EMBL/GenBank Accession Number L05186)) was modified such that the resulting protein when translated had a 6-histidine tag at the N-terminus immediately preceding the start methionine. Active FAK protein has been previously expressed in a baculovirus system using a similar N-terminal 6-histidine tag (Protein Expression And Purification, 1996, 7: 12-18). The human FAK cDNA was cloned into the baculovirus transplacement vector, pFastbac 1 (Life Technologies), and the recombinant construct was co-transfected into insect cells (for example Spodoptera frugiperda 21(Sf21)) with viral DNA to prepare recombinant baculovirus (details of the methods for the assembly of recombinant DNA molecules and the preparation and use of recombinant baculovirus can be found in standard texts for example Sambrook et al, 1989, Molecular cloning - A Laboratory Manual, 2nd edition, Cold Spring Harbour Laboratory Press and O'Reilly et al, 1992, Baculovirus Expression Vectors - A Laboratory Manual, W. H. Freeman and Co, New York. Details specific to the use of the pFastbac ('Bac to Bac') system are provided in Anderson et al., 1995, FOCUS (Life Technologies Bulletin Magazine), 17, p53.)

For expression of biologically active human FAK protein, Sf21 cells were infected with plaque-pure FAK recombinant virus at a multiplicity of infection of 3 and harvested 48 hours later. Harvested cells were washed with ice cold phosphate buffered saline solution (PBS) (10mM sodium phosphate pH7.4, 138mM sodium chloride, 2.7mM potassium chloride) then resuspended in ice cold lysis buffer (50mM HEPES pH7.5, 1mM Dithiothreitol, 100uM Sodium Fluoride, 100uM Sodium Orthovanadate, 10mM Glycerophosphate, 100uM Phenylmethylsulphonylfluoride (PMSF), 5ug/ml Aprotinin, 5ug/ml Leupeptin, 1% Tween; the PMSF being added just before use from a freshly-prepared 100mM solution in methanol) using 250ul lysis buffer per 10 million cells. The suspension was then incubated on ice for 15 minutes

and centrifuged for 10 minutes at 13,000 rpm at 4°C. The supernatant (enzyme stock) was removed and aliquots made which were snap frozen in liquid nitrogen and then stored at -70°C. For a typical batch, stock enzyme was diluted 1 in 250 with enzyme diluent ((100mM HEPES pH 7.4, 0.2mM Dithiothreitol, 200uM Sodium Orthovanadate, 0.1% Triton X-100) and 50ml of freshly diluted enzyme was used for each assay well (see FAK3 protocol, below).

FAK3: In vitro Enyme assay Protocol

A stock of substrate solution was prepared from a random copolymer containing tyrosine, for example Poly (Glu, Ala, Tyr) 6:3:1 (Sigma P3899), stored as 1 mg/ml stock in PBS at -20°C and diluted 1 in 500 with PBS for plate coating.

On the day before the assay 100µl of diluted substrate solution was dispensed into all wells of assay plates (Maxisorp 96 well immunoplates Life technologies, Cat. No. 439454A) which were sealed with plate sealers and left overnight at 4°C.

On the day of the assay the substrate solution was discarded and the assay plate wells were washed once with 200ul PBST (PBS containing 0.05% v/v Tween 20) and once with 200ul 50mM Hepes pH7.4.

Test compounds were made up as 10mM or 30mM stocks in DMSO and then further diluted in glass distilled water diluted to a concentration 10 fold higher than the final assay concentration. 10µl of diluted compound was transferred to wells in the washed assay plates. "No compound" control wells contained 10ul glass distilled water instead of compound.

Forty microlitres of 25mM manganese chloride containing 6.25µM adenosine-5'-triphosphate (ATP) was added to all test wells. To start the reactions 50µl of freshly diluted enzyme was added to each well and the plates were incubated at 23C for 90 minutes. Then the reaction was stopped by adding 100ul of PBS containing 20mM EDTA. The liquid was then discarded and the wells were washed twice with PBST.

One hundred microlitres of mouse HRP-linked anti-phosphotyrosine antibody (Santa Cruz, Product SC 7020-HRP), diluted 1 in 1500 with PBST containing 0.5% w/v bovine serum albumin (BSA), was added to each well and the plates were incubated for 1 hour at room temperature before discarding the liquid and washing the wells twice with 200ul PBST. One hundred microlitres of 2,2'-azino-bis(3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) solution, freshly prepared using one 50mg ABTS tablet (Boehringer 1204 521) in 50ml freshly prepared 50mM phosphate-citrate buffer pH5.0 + 0.03% sodium perborate (made with 1 phosphate

citrate buffer with sodium perborate (PCSB) capsule (Sigma P4922) per 100ml distilled water), was added to each well. Plates were then incubated for 20-60 minutes at room temperature until the absorbance value of the "no compound" control wells, measured at 405nm using a plate reading spectrophotometer, was approximately 1.0.

Dose response curves were generated from the absorbance readings using Origin Software. Compounds were ranked for potency using the Inhibitory Concentration 50 (IC50), as defined by Origin Software analysis.

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) in the above assays may be demonstrated at IC_{50} concentrations or doses in the range 250 μM to 1nM.

When tested in the above *in vitro* assay the CDK4 inhibitory activity of Example 3 was measured as IC_{50} = 0.07μM and that of Example 5 as IC_{50} = 0.02μM. When tested in the above *in vitro* assay the FAK inhibitory activity of Example 6 was measured as IC_{50} = 0.032μM and that of Example 220 as IC_{50} = 0.07μM.

The in-vivo activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity. For example, further details may be found in the following references:-

a) Attenution of the Expression of the Focal Adhesion Kinase induces Apoptosis in Tumor Cells. Xu L-h et al. Cell Growth & Differentiation (1996) 7, p413-418;

b) The COOH-Terminal Domain of the Focal Adhesion Kinase Induces Loss of Adhesion and Cell Death in Human Tumour Cells. Xu L-h et al. Cell Growth & Differentiation (1998) 9, p999-1005;

c) Inhibition of pp125-FAK in Cultured Fibroblasts Results in Apoptosis. Hungerford J.E et al. The Journal of Cell Biology (1996) 135, p1383-1390;

d) Inhibition of Focal Adhesion Kinase (FAK) Signalling in Focal Adhesions Decreases Cell Motility and Proliferation. Gilmore A.P and Romer L.H. Molecular Biology of the Cell (1996) 7, p1209-1224.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M. R. (1989) Status of the NCI preclinical antitumour

drug discovery screen. Prin. Prac Oncol 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth:-

Cells were plated in appropriate medium in a volume of 100µl in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100µl SRB dye (0.4% SRB in 1% acetic acid) was added for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The pyrimidine will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately

0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the pyrimidine derivatives defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property (without being bound by theory) is believed to arise from their (G1-S phase) CDK inhibitory properties. The compounds are also effective inhibitors of FAK. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK and/or FAK enzymes, i.e. the compounds may be used to produce a CDK and/or FAK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation and/or migration of malignant cells characterised by inhibition of CDK and/or FAK enzymes, i.e. the compounds may be used to produce an anti-proliferative/migration effect mediated alone or in part by the inhibition of CDKs and/or FAK. The compounds may also be useful as FAK inhibitors by inducing cell-death (apoptosis). Such a pyrimidine derivative of the invention is expected to possess a wide range of anti-cancer properties as CDKs and/or FAK have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a pyrimidine derivative of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a pyrimidine derivative of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and

recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDK and/or FAK, especially those tumours which are significantly dependent on CDK and/or FAK for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a pyrimidine derivative of the present invention will possess activity against other cell-proliferation/migration diseases in a wide range of other disease states including leukemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal such as man. Particularly, a cell cycle inhibitory effect is produced at the G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

According to a further feature of this aspect of the invention there is provided a method for producing an anti-cancer, cell cycle inhibitory (anti-cell-proliferation) effect and/or a FAK inhibitory (anti-cell migration and/or apoptosis inducing) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a pyrimidine derivative as defined immediately above. Particularly, an inhibitory effect is produced at the G1-S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK4 and CDK6.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit

dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK and/or FAK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere);

topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a pyrimidine derivative of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer. An anti-emetic may also be usefully administered, for example when using such conjoint treatment as described above.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and in vivo test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at ambient temperature, typically in the range 18-25°C and in air unless stated, or unless the skilled person would otherwise operate under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or on Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica, obtained from E. Merck, Darmstadt, Germany; bond elute chromatography was performed using Varian Mega Bond Elut cartridges (10 g, order code 1225-6034), obtained from Varian Sample Preparation Products, California, USA;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic

resonance chemical shift values were measured in deuterated DMSO-δ_6 (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane) using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz, or a Bruker AM250 spectrometer operating at a field strength of 250MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; mass spectrometry (MS) was performed by electrospray on a VG platform;

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on a Waters Spherisorb ODS1 25 cm column, at a flow rate of 2 ml/minute using acetonitrile/water/trifluoroacetic acid (60:40:0.1 v/v) as eluent, detection was at a wavelength of 254 nm, and data are quoted as retention time (RT) in minutes;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions are dried magnesium sulphate was the drying agent;

(ix) the following abbreviations may be used hereinbefore or hereinafter:-

DCM	dichloromethane;
DMF	*N,N*-dimethylformamide;
DMSO	dimethylsulphoxide;
NMP	*N*-methylpyrrolidin-2-one;
THF	tetrahydrofuran.

Example 1

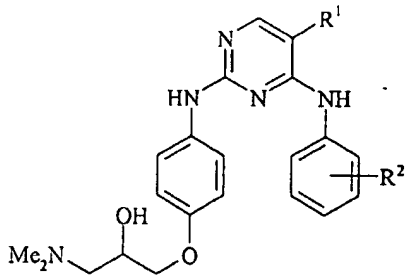
5-Bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-(indan-5-ylamino)pyrimidine

A hot solution of 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89, 156 mg, 0.56 mmol) in methanol (2 ml) was added to a solution of 5-bromo-2-chloro-4-(indan-5-ylamino)pyrimidine (Method 15, 200 mg, 0.62 mmol) in *n*-butanol (20 ml). The mixture was heated at 100°C for 18 hours and silica (1 g) was added. Volatile material was removed by evaporation and the residue was purified by column chromatography, eluting with 0-10% 2.0M methanolic ammonia solution in DCM, to give the product as a colourless

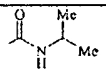
solid (117 mg, 42%). NMR: 2.03 (m, 2H), 2.18 (s, 6H), 2.32 (m, 2H), 2.83 (m, 4H), 3.80 (m, 3H), 4.76 (d, 1H), 6.70 (d, 2H), 7.17 (m, 1H), 7.23 (m, 1H), 7.41 (m, 3H), 8.10 (s, 1H), 8.35 (s, 1H), 9.03 (s, 1H); MS (MH^+): 498.4, 500.4.

Examples 2-41

The following compounds were prepared by an analogous method to that described in Example 1, using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride and the appropriate 5-substituted 4-anilino-2-chloropyrimidine (Methods 7, 9, 11-45, 62-64, or obtained as described in J. Chem. Soc. Perkin Trans. I, 1974, 1970):



Ex	R^1	R^2	NMR	MS (MH^+)
2	Me	H	2.09 (s, 3H), 2.18 (s, 6H), 2.30 (m, 2H), 3.78 (m, 3H), 4.76 (d, 1H), 6.76 (d, 2H), 7.02 (t, 1H), 7.29 (t, 2H), 7.52 (d, 2H), 7.69 (d, 2H), 7.83 (s, 1H), 8.17 (s, 1H), 8.72 (s, 1H)	394.2
3	Br	H	2.19 (s, 6H), 2.31 (m, 2H), 3.82 (m, 3H), 4.75 (d, 1H), 6.74 (d, 2H), 7.12 (t, 1H), 7.34 (t, 2H), 7.43 (d, 2H), 7.61 (d, 2H), 8.16 (s, 1H), 8.44 (s, 1H), 9.09 (s, 1H)	458.3, 460.3
4	Br	2-Ph	2.18 (s, 6H), 2.31 (m, 2H), 3.80 (m, 3H), 4.74 (d, 1H), 6.63 (d, 2H), 7.36 (m, 10H), 7.68 (d, 1H), 7.98 (s, 1H), 8.20 (s, 1H), 8.98 (s, 1H)	534.5, 536.5

5	Br	2-F, 5-Me	2.18 (s, 6H), 2.29 (m, 5H), 3.78 (m, 3H), 4.73 (d, 1H), 6.62 (d, 2H), 7.09 (m, 1H), 7.18 (m, 1H), 7.34 (m, 3H), 8.14 (s, 1H), 8.38 (s, 1H), 9.05 (s, 1H)	490.4, 492.4
6	NO_2	2-F	2.19 (s, 6H), 2.31 (m, 2H), 3.82 (m, 3H), 4.77 (br, 1H), 6.67 (m, 2H), 7.22 (m, 1H), 7.37 (m, 4H), 7.68 (m, 1H), 9.03 (s, 1H)	443.4
7		H	1.18 (d, 6H), 2.18 (s, 6H), 2.32 (m, 2H), 3.83 (m, 3H), 4.08 (m, 1H), 4.76 (d, 1H), 6.81 (d, 2H), 7.04 (t, 1H), 7.29 (t, 2H), 7.52 (d, 2H), 7.63 (d, 2H), 8.16 (d, 1H), 8.64 (s, 1H), 9.43 (s, 1H)	465.5
8	Br	2-Br, 4-Me	2.18 (s, 6H), 2.31 (m, 5H), 3.78 (m, 3H), 4.75 (d, 1H), 6.60 (d, 2H), 7.24 (m, 3H), 7.58 (m, 2H), 8.12 (s, 1H), 8.39 (s, 1H), 9.06 (s, 1H)	550.4, 552.4, 554.4
9	Br	2-morpholino	2.18 (s, 6H), 2.31 (m, 2H), 2.82 (m, 4H), 3.80 (m, 5H), 3.90 (m, 2H), 4.76 (br, 1H), 6.83 (d, 2H), 7.08 (m, 2H), 7.30 (m, 1H), 7.49 (d, 2H), 8.19 (s, 1H), 8.82 (s, 1H), 9.20 (s, 1H)	543.5, 545.5
10	Br	4-Br	2.18 (s, 6H), 2.32 (m, 2H), 3.83 (m, 3H), 4.76 (d, 1H), 6.77 (d, 2H), 7.40 (d, 2H), 7.46 (m, 2H), 7.59 (m, 2H), 8.16 (s, 1H), 8.38 (s, 1H), 9.10 (s, 1H)	536.5, 538.4, 540.4
11	Me	3-Cl	2.08 (s, 3H), 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.73 (br s, 1H), 6.78 (d, 2H), 7.04 (d, 2H), 7.30 (dd, 1H), 7.49 (d, 2H), 7.69 (d, 1H), 7.82 (s, 1H), 7.87 (s, 1H), 8.28 (s, 1H), 8.80 (s, 1H)	428.2, 430.2

12	Me	3,4-di-Cl	2.07 (s, 3H), 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.74 (br s, 1H), 6.80 (d, 2H), 7.45-7.55 (m, 3H), 7.74 (dd, 1H), 7.89 (s, 1H), 8.05 (d, 1H), 8.37 (s, 1H), 8.84 (s, 1H)	461.8, 463.7
13	Cl	H	2.18 (s, 6H), 2.30 (m, 2H), 3.82 (m, 3H), 4.76 (d, 1H), 6.77 (d, 2H), 7.12 (t, 1H), 7.34 (t, 2H), 7.46 (d, 2H), 7.64 (d, 2H), 8.07 (s, 1H), 8.71 (s, 1H), 9.07 (s, 1H)	414.4, 416.4
14	Cl	2-Cl, 5-Me	2.18 (s, 6H), 2.30 (m, 5H), 3.79 (m, 3H), 4.76 (d, 1H), 6.62 (d, 2H), 7.10 (m, 1H), 7.31 (d, 2H), 7.42 (d, 1H), 7.54 (s, 1H), 8.06 (s, 1H), 8.55 (s, 1H), 9.08 (s, 1H)	462.4, 464.4, 466.4
15	Cl	2-morpholino	2.19 (s, 6H), 2.33 (m, 2H), 2.82 (s, 4H), 3.82 (m, 7H), 4.77 (d, 1H), 6.83 (d, 2H), 7.09 (m, 2H), 7.38 (m, 1H), 7.49 (m, 2H), 8.16 (s, 1H), 8.48 (m, 1H), 8.80 (s, 1H), 9.21 (s, 1H)	499.5, 501.5
16	Cl	4-Br	2.19 (s, 6H), 2.33 (m, 2H), 3.84 (m, 3H), 4.77 (d, 1H), 6.78 (d, 2H), 7.42 (m, 4H), 7.63 (d, 2H), 8.09 (s, 1H), 8.82 (s, 1H), 9.12 (s, 1H)	492.4, 494.4, 496.4,
17	Br	2-$PhCH_2$-	2.15 (s, 6H), 2.3 (m, 2H), 3.7 (m, 1H), 3.85 (m, 2H), 3.9 (s, 2H), 4.7 (d, 1H), 6.6 (d, 2H), 7.0-7.3 (m, 10H), 7.4 (d, 1H), 8.05 (s, 1H), 8.25 (s, 1H), 9.0 (s, 1H)	548, 550
18	Br	2-PhO-	2.8 (s, 6H), 3.2 (m, 2H), 3.9 (m, 2H), 4.2 (s, 1H), 5.9 (s, 1H), 6.8 (d, 2H), 6.95 (m, 3H), 7.1 (t, 1H), 7.2 (m, 2H), 7.3 (t, 2H), 7.45 (d, 2H), 8.05 (s, 1H), 8.1 (m, 1H), 9.2 (s, 1H)	550, 552

19	Br	2-$PhCH_2O$-	2.2 (s, 6H), 2.4 (m, 2H), 3.8 (m 1H), 3.9 (m, 2H), 4.8 (s, 1H), 5.2 (s, 2H), 6.8 (d, 2H), 6.95 (t, 1H), 7.1 (t, 1H), 7.2 (m, 1H), 7.3 (m, 3H), 7.55 (m, 4H), 8.1 (s, 1H), 8.2 (m, 2H), 9.2 (s, 1H)	564, 566
20	NO_2	H	2.1 (s, 6H), 2.3 (m, 2H), 3.8-4.0 (m, 3H), 4.8 (d, 1H), 6.7 (m, 2H), 7.15 (t, 1H), 7.4 (m, 4H), 7.6 (d, 2H), 9.1 (s, 1H)	425
21	F	H	2.19 (s, 6H), 2.34 (m, 2H), 3.82 (m, 3H), 4.76 (d, 1H), 6.79 (d, 2H), 7.03 (t, 1H), 7.30 (t, 2H), 7.50 (d, 2H), 7.77 (d, 2H), 8.03 (d, 1H), 8.94 (s, 1H), 9.22 (s, 1H)	398.4
22	F	2-Cl, 5-Me	2.17 (s, 6H), 2.30 (m, 5H), 3.78 (m, 3H), 4.76 (d, 1H), 6.62 (d, 2H), 7.09 (m, 1H), 7.39 (m, 4H), 8.02 (d, 1H), 8.89 (m, 2H)	446.4, 448.4
23	F	2-morpholino	2.18 (s, 6H), 2.34 (m, 2H), 2.83 (m, 4H), 3.71 (m, 4H), 3.82 (m, 3H), 4.76 (d, 1H), 6.80 (d, 2H), 7.09 (m, 2H), 7.26 (m, 1H), 7.51 (d, 2H), 8.07 (d, 1H), 8.33 (m, 1H), 8.50 (d, 1H), 9.03 (s, 1H)	483.5
24	F	4-Br	2.18 (s, 6H), 2.32 (m, 2H), 3.78 (m, 3H), 4.77 (d, 1H), 6.81 (d, 2H), 7.44 (m, 4H), 7.76 (m, 2H), 8.07 (d, 1H), 8.98 (s, 1H), 9.38 (s, 1H)	476.4, 478.4
25	morpholino	H	2.8 (m, 10H), 3.2 (m, 2H), 3.8 (m, 4H), 3.9 (s, 2H), 4.2 (s, 1H), 5.9 (s, 1H), 6.8 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.6 (d, 2H), 7.8 (d, 2H), 8.0 (s, 1H), 8.3 (s, 1H), 8.9 (s, 1H)	465.5
26	Br	4-$PhCH_2O$-	2.35 (s, 6H), 2.6 (m, 2H), 3.8 (m, 2H), 4.0 (m, 1H), 5.1 (s, 2H), 6.6 (d, 2H), 7.0 (d, 2H), 7.3-7.5 (m, 9H), 8.1 (s, 1H), 8.4 (s, 1H), 9.05 (s, 1H)	564, 566

27	Br	3-PhO-	2.15 (s, 6H), 2.3 (m, 2H), 3.7-3.9 (m, 3H), 4.7 (s, 1H), 6.7 (m, 3H), 7.0-7.2 (m, 3H), 7.3-7.6 (m, 7H), 8.2 (s, 1H), 8.5 (s, 1H), 9.1 (s, 1H)	550, 552
28	Br	4-PhO-	2.5 (s, 6H), 2.8 (m, 2H), 3.8 (m, 1H), 4.0 (m, 2H), 6.7 (d, 2H), 7.0 (m, 4H), 7.1 (t, 1H), 7.4 (m, 4H), 7.6 (d, 2H), 8.1 (s, 1H), 8.5 (s, 1H), 9.1 (s, 1H)	550, 552
29	Br	3-$PhCH_2O$-	2.1 (s, 6H), 2.3 (m, 2H), 3.75 (m, 1H), 3.85 (m, 2H), 4.65 (s, 1H), 5.0 (s, 2H), 6.75 (m, 3H), 7.2-7.5 (m, 10H), 8.15 (s, 1H), 8.3 (s, 1H), 9.1 (s, 1H)	564, 566
30'	Br	4-$PhCH_2$-	2.8 (s, 6H), 3. 2 (m, 2H), 3.85 (m 2H), 3.95 (s, 2H), 4.2 (s, 1H), 5.9 (d, 1H), 6.7 (d, 2H), 7.1-7.3 (m, 7H), 7.5 (t, 4H), 8.1 (s, 1H), 8.35 (s, 1H), 9.1 (s, 1H)	548, 550
31	Cl	3,4-di-Cl	2.19 (s, 6H), 2.34 (m, 2H), 3.84 (m, 3H), 4.76 (br, 1H), 6.80 (d, 2H), 7.41 (d, 2H), 7.50 (d, 1H), 7.69 (m, 1H), 8.00 (m, 1H), 8.14 (s, 1H), 8.9 (s, 1H), 9.19 (s, 1H)	482.4, 484.4, 486.4
32	Cl	2-F, 5-Me	2.18 (s, 6H), 2.28 (m, 5H), 3.79 (m, 3H), 4.76 (d, 1H), 6.62 (d, 2H), 7.14 (m, 2H), 7.32 (m, 3H), 8.05 (s, 1H), 8.61 (s, 1H), 9.07 (s, 1H)	446.4, 448.4
33	Cl	3,4-$(CH_2)_3$ **	2.03 (m, 2H), 2.18 (s, 6H), 2.31 (m, 2H), 2.82 (m, 4H), 3.82 (m, 3H), 4.76 (d, 1H), 6.74 (d, 2H), 7.16 (d, 1H), 7.28 (m, 1H), 7.43 (d, 2H), 7.49 (br, 1H), 8.04 (s, 1H), 8.59 (s, 1H), 9.03 (s, 1H)	454.5, 456.5
34	Cl	2-CN	2.18 (s, 6H), 2.30 (m, 2H), 3.78 (m, 3H), 4.76 (d, 1H), 6.62 (d, 2H), 7.27 (d, 2H), 7.43 (m, 1H), 7.62 (m, 1H), 7.74 (m, 1H), 7.88 (m, 1H), 8.12 (s, 1H), 9.13 (s, 1H), 9.19 (br, 1H)	439.4, 441.4

35	$PhCH_2$-	H	2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 3.92 (s, 2H), 4.73 (br s, 1H), 6.74 (d, 2H), 7.01 (t, 1H), 7.1-7.35 (m, 7H), 7.50 (d, 2H), 7.62 (d, 2H), 7.79 (s, 1H), 8.17 (s, 1H), 8.81 (s, 1H)	470.5
36	EtO-	H	1.4 (t, 3H), 2.2 (s, 6H), 2.25 (dd, 1H), 2.4 (dd, 1H), 3.75-3.9 (m, 3H), 4.05 (q, 2H), 6.8 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.8 (s, 1H), 7.85 (d, 2H), 8.4 (s, 1H), 8.65 (s, 1H)	424.5
37	Br	4-$HOCH_2$-	2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.49 (d, 2H), 4.74 (d, 1H), 5.13 (t, 1H), 6.74 (d, 2H), 7.27 (d, 2H), 7.44 (d, 2H), 7.54 (d, 2H), 8.13 (s, 1H), 8.43 (s, 1H), 9.07 (s, 1H)	488.1, 490.1
38[2]	Br	4-^{n}BuOCH_2-	0.89 (t, 3H), 1.36 (tq, 2H), 1.54 (tt, 2H), 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.44 (t, 2H), 3.75-3.9 (m, 3H), 4.44 (s, 2H), 4.78 (d, 1H), 6.74 (d, 2H), 7.29 (d, 2H), 7.45 (d, 2H), 7.59 (d, 2H), 8.17 (s, 1H), 8.53 (s, 1H), 9.13 (s, 1H)	544.6, 546.6
39	CH_2=CH-	H	2.2 (s, 6H), 2.3 (dd, 1H), 2.4 (dd, 1H), 3.75-3.95 (m, 3H), 4.75 (br d, 1H), 5.15 (d, 1H), 5.6 (d, 1H), 6.75 (d, 2H), 6.95 (dd, 1H), 7.05 (t, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.65 (d, 2H), 8.25 (s, 1H), 8.6 (s, 1H), 9.0 (s, 1H)	406.5
40	MeO	H	2.2 (s, 6H), 2.3 (dd, 1H), 2.4 (dd, 1H), 3.8-4.0 (m, 6H), 6.8 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.6 (d, 2H), 7.8 (s, 1H), 7.85 (d, 2H), 8.6 (s, 1H), 8.65 (s, 1H)	410.4
41[3]	CN	H	2.17 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.76 (d, 1H), 6.76 (br d, 2H), 7.14 (t, 1H), 7.34 (dd, 2H), 7.45 (d, 2H), 7.55 (br d, 2H), 8.44 (s, 1H), 9.39 (br s, 1H), 9.71 (br s, 1H)	405.4

[1] Isolated as hydrochloride salt.

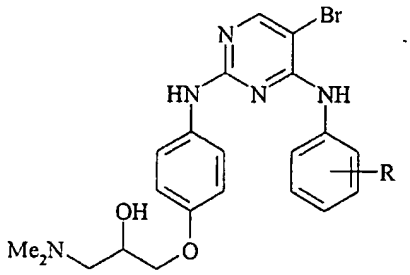
[2] Obtained as a by-product from Example 37 by evaporation of the less polar chromatography fractions.

[3] Prepared from 4-anilino-5-cyano-2-(methanesulphonyl)pyrimidine (Method 64).

** Such that R^2 and the phenyl ring to which it is attached forms indan-5-yl.

Examples 42-43

The following compounds were prepared by an analogous method to that described in Example 1, using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride and the appropriate 4-anilino-5-bromo-2-chloropyrimidine (Methods 46-47):



Ex	R	MS (MH^+)	HPLC (RT) [1]
42[2]	3-CF_3	526, 528	1.75
43	4-CF_3	526, 528	1.74

[1] Data obtained from a Hypersil 10 cm base deactivated reverse phase column, using 5-95% acetonitrile/water gradient, flow rate 1 ml/min over 10 minutes.

[2] The product obtained after chromatography was washed with *t*-butylmethylether.

Example 44

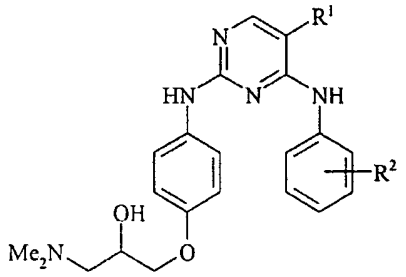
5-Bromo-4-(3-chloroanilino)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine

A solution of 5-bromo-2,4-dichloropyrimidine (228 mg, 1.0 mmol), 3-chloroaniline (140 mg, 1.1 mmol) and *N,N*-diisopropylethylamine (148 mg, 1.15 mmol) in *n*-butanol (10 ml) was heated at 100°C for 6 hours. A solution of 4-[2-hydroxy-3-(*N,N*-dimethylamino) propoxy]aniline hydrochloride (Method 89, 250 mg, 0.90 mmol) in methanol (3 ml) was

added and the solution was heated at 100°C for 20 hours and then concentrated to a volume of 5 ml. The solution was loaded on a Varian Mega Bond Elut column and the column was eluted with 0-4% 2.0M methanolic ammonia solution in DCM. Concentration of the appropriate fractions and recrystallization of the residue from a mixture of acetonitrile and ether gave the product, isolated as a hydrochloride salt (110 mg, 21%). NMR: 2.8 (s, 6H), 3.05-3.3 (m, 2H), 3.8-3.9 (m, 2H), 4.25-4.3 (m, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 7.15 (d, 1H), 7.35 (t, 1H), 7.5 (d, 2H), 7.6 (d, 1H), 7.75 (s, 1H), 8.2 (s, 1H), 8.6 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H); MS (MH^+): 492, 494, 496.

Examples 45-78

The following compounds were prepared by an analogous method to that described in Example 44, using the appropriate 5-substituted 2,4-dichloropyrimidine, the appropriate substituted aniline and 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89).



Ex	R^1	R^2	NMR	MS (MH^+)
45	Br	4-F	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.9 (m, 2H), 4.25 (m, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 7.2 (t, 2H), 7.4 (d, 2H), 7.6 (m, 2H), 8.15 (s, 1H), 8.6 (s, 1H), 9.15 (s, 1H), 9.75 (br s, 1H)	476, 478

46	Br	4-MeO-	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.8 (s, 3H), 3.9 (m, 2H), 4.25 (m, 1H), 5.9 (d, 1H), 6.7 (d, 2H), 6.9 (d, 2H), 7.5 (dd, 4H), 8.1 (s, 1H), 8.4 (1H), 9.05 (s, 1H), 9.8 (br s, 1H)	488, 490
47	Br	4-Cl	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.9 (m, 2H), 4.25 (m, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 7.35 (d, 2H), 7.45 (d, 2H), 7.65 (d, 2H), 8.2 (s, 1H), 8.6 (1H), 9.2 (s, 1H), 9.8 (br s, 1H)	492, 494, 496
48	Br	3-Cl, 4-F	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.9 (m, 2H), 4.25 (m, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 7.35-7.45 (m, 3H), 7.6 (m, 1H), 7.85 (m, 1H), 8.2 (s, 1H), 8.65 (1H), 9.2 (s, 1H), 9.7 (br s, 1H)	510, 512, 514
49	Br	4-"BuO-	0.95 (t, 3H), 1.4-1.45 (m, 2H), 1.55-1.6 (m, 2H), 2.8 (m, 6H), 3.05-3.15 (m, 2H), 3.9 (m, 2H), 4.0 (t, 2H), 4.2 (m, 1H), 5.9 (br s, 1H), 6.75 (d, 2H), 6.9 (d, 2H), 7.4 (t, 4H), 8.1 (s, 1H), 8.4 (s, 1H), 9.05 (s, 1H), 9.8 (br s, 1H)	530, 532
50[1]	Br	3,4-CH=N-NH- **	2.8 (dd, 6H), 3.1-3.3 (m, 2H), 3.8-3.9 (m, 2H), 4.2-4.3 (m, 1H), 6.6 (d, 2H), 7.3 (d, 2H), 7.4 (dd, 1H), 7.6 (d, 1H), 7.85 (s, 1H), 8.1 (s, 1H), 8.35 (s, 1H), 9.75 (br s, 1H), 9.9 (br s, 1H), 10.2-10.4 (br s, 1H)	498, 500
51	Br	2-F	2.8 (s, 6H), 3.05-3.15 (m, 2H), 3.8-3.9 (m, 2H), 4.2-4.25 (m, 1H), 5.9 (d, 1H), 6.65 (d, 2H), 7.2 (m, 1H), 7.3-7.4 (m, 3H), 7.5-7.6 (t, 1H), 8.15 (s, 1H), 8.5 (s, 1H), 9.15 (s, 1H), 9.8 (br s, 1H)	476, 478
52	Br	2-MeO-	2.7 (s, 6H), 2.9-3.2 (m, 2H), 3.8 (s, 3H), 3.95 (d, 2H), 4.2 (m, 1H), 6.8 (d, 2H), 6.9 (m, 1H), 7.1 (m, 2H), 7.4 (d, 2H), 7.4-7.9 (br s, 1H), 8.0 (s, 1H), 8.15 (br s, 1H), 8.2 (s, 1H) 9.2 (s, 1H)	488, 490

53	Br	3-MeO-	2.8 (s, 6H), 3.1-3.3 (m, 2H), 3.7 (s, 3H), 3.8-4.0 (m, 2H), 4.15 (m, 1H), 5.9 (d, 1H), 6.7 (m, 1H), 6.8 (d, 2H), 7.2 (m, 3H), 7.5 (d, 2H), 8.15 (s, 1H), 8.4 (s, 1H), 9.2 (s, 1H), 9.8-10.0 (br s, 1H)	488, 490
54	Br	2-Cl	2.8 (s, 6H), 3.1-3.3 (m, 2H), 3.8-3.9 (m, 2H), 4.3 (m, 1H), 5.95 (d, 1H), 6.7 (d, 2H), 7.2-7.5 (m, 3H), 7.6-7.7 (d, 1H), 7.8 (d, 1H), 8.2 (s, 1H), 8.5 (s, 1H) 9.25 (s, 1H), 9.6-9.8 (br s, 1H)	492, 494, 496
55	Br	4-Cl, 2-F	2.8 (s, 6H), 3.1-3.3 (m, 2H), 3.8-4.0 (m, 2H), 4.3 (m, 1H), 5.9 (m, 1H), 6.7 (d, 2H), 7.35 (d, 2H), 7.5-7.6 (m, 2H), 8.2 (s, 1H), 8.7 (s, 1H), 9.2 (s, 1H), 9.7-9.9 (br s, 1H)	510, 512, 514
56	Br	4-Br, 2-F	2.8 (s, 6H), 3.05-3.2 (m, 2H), 3.8-3.9 (m, 2H), 4.2 (br d, 1H), 5.8-6.0 (br s, 1H), 6.7 (d, 2H), 7.3 (d, 2H), 7.4-7.5 (m, 2H), 7.65 (d, 1H), 8.2 (s, 1H), 8.6 (s, 1H), 9.15 (s, 1H)	554, 556, 558
57	Br	3-F	2.8 (s, 6H), 3.05-3.2 (m, 2H), 3.9-4.0 (m, 2H), 4.2-4.3 (m, 1H), 5.9- (d, 1H), 6.8 (d, 2H), 6.9 (m, 1H), 7.3 (m, 1H), 7.4-7.5 (m, 2H), 7.65 (d, 1H), 8.2 (s, 1H), 8.6 (s, 1H), 9.15 (s, 1H), 9.7-9.8 (br s, 1H)	476, 478
58	Br	2-F, 4-Me	2.8 (s, 6H), 3.1-3.2 (m, 2H), 3.8-3.9 (m, 2H), 4.2 (br s, 1H), 5.9 (br s, 1H) 6.65 (d, 2H) 7.0 (d, 1H), 7.15 (d, 1H), 7.35-7.4 (m, 3H), 8.1 (s, 1H), 8.45 (s, 1H), 9.1 (s, 1H)	490, 492
59	Br	2,4-di-F	2.8 (S, 6H) 3.05-3.15 (d, 2H), 3.8 (m, 2H), 4.25 (br s, 1H), 5.9 (br d, 1H), 6.65 (d, 2H), 7.05 (t, 1H), 7.25 (d, 2H), 7.3-7.6 (m, 2H), 8.15 (s, 1H), 8.6 (s, 1H), 9.1 (s, 1H), 9.7-9.8 (br s, 1H)	494, 496

60	Br	2,5-di-F	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.8-4.0 (m, 2H), 4.2 (m, 1H), 5.9 (d, 1H), 6.75 (d, 2H), 7.1 (m, 1H), 7.4 (m, 3H), 7.6 (m, 1H), 8.2 (s, 1H), 8.5 (s, 1H), 9.2 (s, 1H), 9.7-9.8 (br s, 1H)	494, 496
61	Br	2,5-di-Me	2.1 (s, 3H), 2.3 (s, 3H), 2.8 (s, 6H), 3.1-3.3 (m, 2H), 3.8-3.9 (m, 2H), 4.2-4.3 (m, 1H), 5.9 (d, 1H), 6.6 (d, 2H), 7.0 (d, 1H), 7.2 (m, 2H), 7.35-7.4 (d, 2H), 8.05 (s, 1H), 8.3 (s, 1H), 9.05 (s, 1H), 9.8 (br s, 1H)	486, 488
62[2]	Br	3,4-CH=CH-NH- ##	2.2 (s, 6H), 2.2-2.4 (m, 2H), 3.7 (m, 1H), 3.8 (m, 2H), 4.7 (d, 2H), 6.4 (t, 1H), 6.6 (d, 2H), 7.15 (dd, 1H), 7.3-7.4 (m, 3H), 7.7 (d, 1H), 8.1 (s, 1H), 8.4 (s, 1H), 9.0 (s, 1H), 11.05 (br s, 1H)	496, 498
63[2]	Br	3,4-CH=CH-CH=N- ^^	2.2 (s, 6H), 2.2-2.45 (m, 2H), 3.7 (m, 1H), 3.85 (m, 2H), 4.8 (br s, 1H), 6.65 (d, 2H), 7.4 (d, 2H), 7.5 (m, 1H), 7.95 (q, 4H), 8.15 (d, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 8.8 (m, 2H), 9.2 (s, 1H)	509, 511
64	Cl	3-F	2.8 (s, 6H), 3.15-3.25 (m, 2H), 3.9 (m, 2H), 4.25 (br s, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 6.9 (m, 1H), 7.35 (m, 1H), 7.5 (m, 3H), 7.7 (d, 1H), 8.15 (s, 1H), 8.9 (s, 1H), 9.25 (s, 1H), 9.8 (br s, 1H)	432, 434
65	Cl	4-F	2.8 (s, 6H), 3.15-3.2 (m, 2H), 3.9 (m, 2H), 4.3 (br s, 1H), 5.9 (d, 1H), 6.8 (d, 2H), 7.2 (t, 2H), 7.5 (d, 2H), 7.65 (m, 2H), 8.1 (s, 1H), 8.8 (s, 1H), 9.15 (s, 1H), 9.8 (br s, 1H)	432, 434
66	Cl	2,5-di-F	2.9 (s, 6H), 3.1-3.3 (m, 2H), 3.9 (m, 2H), 4.3 (br s, 1H), 6.0 (br s, 1H), 6.8 (m, 1H), 6.9 (d, 2H), 7.2 (m, 1H), 7.4 (m, 1H), 7.5 (d, 2H), 7.7 (m, 1H), 8.1 (s, 1H), 8.8 (s, 1H), 8.85 (s, 1H), 9.9 (br s, 1H)	450, 452

67	Cl	4-MeO-	2.8 (s, 6H), 3.15-3.3 (m, 2H), 3.75 (s, 3H), 3.85 (m, 2H), 4, 25 (br s, 1H), 5.9 (d, 1H), 6.75 (d, 2H), 6.9 (d, 2H), 7.5 (m, 4H), 8.05 (s, 1H), 8.65 (s, 1H), 9.1 (s, 1H), 9.8 (br s, 1H)	444, 446
68	Cl	4-^{n}BuOCH$_2$-	0.9 (t, 3H), 1.3 (m, 2H), 1.5 (m, 2H), 2.8 (d, 6H), 3.1-3.3 (m, 2H), 3.4 (t, 2H), 3.9 (m, 2H), 4.25 (br s, 1H), 4.4 (s, 2H), 5.9 (br s, 1H), 5.9 (s, 1H), 6.8 (d, 2H), 7.3 (d, 2H), 7.5 (d, 2H), 7.6 (d, 2H), 8.1 (s, 1H), 8.8 (s, 1H), 9.2 (s, 1H), 9.8 (br s, 1H)	500, 502
69[3]	Br	4-H$_2$NC(O)-	2.81 (dd, 6H), 3.15-3.30 (m, 2H), 3.91 (m, 2H), 4.28 (m, 1H), 4.75 (br s, 1H), 6.84 (d, 2H), 7.30 (br s, 1H), 7.40 (d, 2H), 7.68 (d, 2H), 7.88 (d, 2H), 7.98 (br s, 1H), 8.31 (s, 1H), 9.28 (br s, 1H), 9.7-9.95 (m, 2H)	501.1, 503.2
70[3]	Br	4-OH	2.81 (dd, 6H), 3.15-3.30 (m, 2H), 3.92 (m, 2H), 4.27 (m, 1H), 6.79 (d, 2H), 6.81 (d, 2H), 7.24 (d, 2H), 7.34 (d, 2H), 8.29 (s, 1H), 9.50 (br s, 1H), 9.83 (br s, 1H), 10.23 (s, 1H)	474.3, 476.3
71	Br	4-HOCH$_2$CH$_2$-	2.18 (s, 6H), 2.2-2.45 (m, 2H), 2.72 (t, 2H), 3.61 (t, 2H), 3.75-3.9 (m, 3H), 4.62 (br s, 1H), 4.74 (br s, 1H), 6.73 (d, 2H), 7.18 (d, 2H), 7.44 (d, 2H), 7.48 (d, 2H), 8.12 (s, 1H), 8.40 (s, 1H), 9.06 (s, 1H)	502.3, 504.3
72	Br	3-HOCH$_2$-	2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.50 (d, 2H), 4.74 (t, 1H), 5.15 (m, 1H), 6.75 (d, 2H), 7.09 (d, 1H), 7.30 (dd, 1H), 7.44 (d, 2H), 7.50 (br s, 2H), 8.15 (s, 1H), 8.44 (s, 1H), 9.08 (s, 1H)	488.2, 490.2

73	Br	2-$HOCH_2$-	2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.56 (s, 2H), 4.74 (d, 1H), 5.62 (br s, 1H), 6.74 (d, 2H), 7.14 (dd, 1H), 7.29 (d, 1H), 7.34 (dd, 1H), 7.43 (d, 2H), 7.94 (d, 1H), 8.17 (s, 1H), 8.91 (br s, 1H), 9.11 (s, 1H)	488.2, 490.2
74[4]	Br	4-H_2NSO_2-	2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.75 (br s, 1H), 6.80 (d, 2H), 7.28 (br s, 2H), 7.46 (d, 2H), 7.74 (d, 2H), 7.87 (d, 2H), 8.13 (s, 1H), 8.75 (s, 1H), 9.20 (s, 1H)	537.2, 539.2
75	Br	4-$CH_3C(O)NH$-	2.04 (s, 3H), 2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.73 (br s, 1H), 6.73 (d, 2H), 7.4-7.55 (m, 6H), 8.11 (s, 1H), 8.43 (s, 1H), 9.06 (s, 1H), 9.91 (s, 1H)	515.2, 517.2
76[5]	Br	4-NH_2	2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.73 (br s, 1H), 4.97 (br s, 2H), 6.57 (d, 2H), 6.70 (d, 2H), 7.11 (d, 2H), 7.44 (d, 2H), 8.03 (s, 1H), 8.17 (s, 1H), 8.96 (s, 1H)	473.3, 475.3
77[6]	Br	4-(2-morpholino-ethoxy)	2.18 (s, 6H), 2.2-2.4 (m, 2H), 2.45-2.5 (m, 4H), 2.70 (t, 2H), 3.55-3.6 (m, 4H), 3.75-3.9 (m, 3H), 4.10 (t, 2H), 4.74 (br s, 1H), 6.72 (d, 2H), 6.93 (d, 2H), 7.41 (d, 2H), 7.43 (d, 2H), 8.09 (s, 1H), 8.39 (s, 1H), 9.00 (s, 1H)	587.4, 589.4
78[7]	Br	4-[2-(imidazol-1-yl)ethoxy]	2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.25 (t, 2H), 4.37 (t, 2H), 4.91 (br s, 1H), 6.70 (d, 2H), 6.90 (s, 1H), 6.92 (d, 2H), 7.24 (s, 1H), 7.40 (d, 2H), 7.44 (d, 2H), 7.69 (s, 1H), 8.09 (s, 1H), 8.40 (s, 1H), 9.01 (s, 1H)	568.3, 570.3

[1] Isolated as dihydrochloride salt.

[2] Isolated as free base.

[3] Isolated as dihydrochloride salt which separated out from the reaction mixture.

[4] Bis-sulphonamide impurity precipitate removed by filtration from reaction mixture.

[5] Obtained as a by-product from Example 75 by evaporation of the less polar chromatography fractions.

[6] Starting 4-[2-(4-morpholino)ethoxy]aniline obtained as described in Eur. Pat. Appl. EP 401358.

[7] Starting 4-[2-(1-imidazolyl)ethoxy]aniline obtained as described in J. Med. Chem., 1985, 28, 1427.

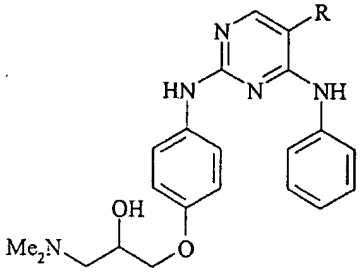
** Such that R^2 and the phenyl ring to which it is attached forms 1H-indazol-5-yl.

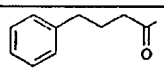
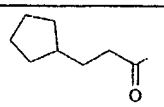
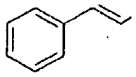
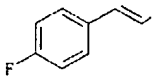
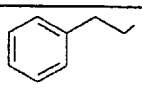
Such that R^2 and the phenyl ring to which it is attached forms indol-5-yl.

^^ Such that R^2 and the phenyl ring to which it is attached forms quinolin-6-yl.

Examples 79-85

The following compounds were prepared by an analogous method to that described in Example 1, using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89) and the appropriate 5-substituted 4-anilino-2-chloropyrimidine intermediate (Methods 66-71, 73).



Ex	R	NMR	MS (MH^+)
79		1.85-2.0 (m, 2H), 2.6-2.75 (t, 2H), 2.8-2.9 (dd, 6H), 2.95-3.0 (t, 2H), 3.15-3.35 (m, 2H), 3.9-4.0 (m, 2H), 4.3 (m, 1H), 4.6-5.0 (br s, 1H), 6.85-6.95 (d, 2H), 7.15-7.4 (m, 9H), 7.45-7.55 (d, 2H), 7.55-7.75 (br s, 2H), 8.9-9.0 (bs, 1H), 9.8-10.0 (br s, 1H)	526
80		1.0-1.2 (m, 2H), 1.4-1.7 (m, 6H), 1.7-1.9 (m, 3H), 2.2 (s, 6H), 2.25-2.4 (m, 2H), 2.95 (t, 2H), 3.8-3.95 (m, 3H), 4.8 (d, 1H), 6.85 (d, 2H), 7.1 (t, 1H), 7.35 (t, 2H), 7.5-7.6 (d, 2H), 7.6-7.8 (br s, 2H), 8.9 (s, 1H), 9.8 (br s, 1H)	504
81	trans 	2.2 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.95 (m, 3H), 4.7 (br s, 1H), 6.7-6.8 (d, 2H), 7.0-7.15 (m, 2H), 7.2-7.4 (m, 6H), 7.4-7.65 (m, 6H), 8.4 (s, 1H), 8.8 (s, 1H), 9.1 (s, 1H)	482
82	trans 	(s, 6H), 2.2-2.4 (m, 2H), 3.8 (m, 1H), 3.85-3.95 (m, 2H), 4.75 (br s, 1H), 6.8 (d, 2H), 7.0-7.15 (m, 2H), 7.2-7.25 (t, 2H), 7.3-7.4 (m, 3H), 7.5 (d, 2H), 7.6-7.7 (m, 4H), 8.4 (s, 1H), 8.8 (s, 1H), 9.1 (s, 1H)	500
83	Ph	2.1 (s, 6H), 2.2-2.5 (m, 2H), 3.7-3.95 (3, H), 4.85 (d, 1H), 6.8 (d, 2H), 7.0 (m, 1H), 7.25 (t, 2H), 7.3-7.6 (m, 10H), 7.9 (s, 1H), 8.1 (s, 1H), 9.0 (s, 1H)	456
84		2.2 (s, 6H), 2.25-2.4 (m, 2H), 2.85 (s, 2H), 3.25 (s, 2H) 3.7-3.9 (m, 3H), 4.7 (d, 1H), 6.7 (d, 2H), 7.0-7.1 (t, 1H), 7.1-7.2 (m, 1H), 7.25-7.4 (m, 6H), 7.5 (d, 2H), 7.65 (d, 2H), 7.8 (s, 1H), 8.3 (s, 1H), 8.75 (s, 1H)	484
85	fur-3-yl	2.8 (m, 6H), 3.1-3.3 (m, 2H), 3.9 (m, 2H), 4.3 (m, 1H), 6.8 (s, 1H), 6.85 (d, 2H), 7.2 (t, 1H), 7.3-7.4 (m, 4H), 7.5 (d, 2H), 7.8 (s, 1H), 8.1 (s, 2H), 9.4 (s, 1H), 10.0 (br s, 1H), 10.5-10.6 (br s, 1H)	446

Example 86

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine

4-[2-Hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89, 12.58 g, 44.5 mmol) was dissolved in boiling methanol (100 ml). The solution was added to a solution of 4-anilino-2-chloro-5-(ethoxymethyl)pyrimidine (Method 48; 13.01 g, 49.4 mmol) in *n*-butanol (400 ml) at 100°C and the mixture was heated at 100°C for 20 hours. Volatile material was removed by evaporation and hc residue was dissolved in ethanol (400 ml). The solution was heated under reflux for 20 hours and then the solvent was removed by evaporation. The residue was dissolved in 10% methanol solution in DCM (50 ml), and loaded on a silica column. The column was eluted with 2-9% methanol solution in DCM containing 0.5% aqueous ammonia solution. Concentration of the appropriate fractions gave the product as a pale orange foam (17.6 g, 91%). NMR ($CDCl_3$): 1.28 (t, 3H), 2.33 (s, 6H), 2.3-2.6 (m, 2H), 3.54 (q, 2H), 3.97 (d, 2H), 4.07 (tt, 1H), 4.48 (s, 2H), 6.87 (d, 2H), 6.89 (s, 1H), 7.08 (t, 1H), 7.31 (dd, 2H), 7.44 (d, 2H), 7.57 (d, 2H), 7.87 (s, 1H), 7.93 (br s, 1H); MS (MH^+): 438.5.

A sample of the di-hydrochloride salt of this example was also prepared. The free base (165 mg, 0.38 mmol) was dissolved in ethyl acetate/diethyl ether (1:3 v/v, 5 ml). Ethereal hydrogen chloride (1.0M; 1.2 ml, 1.2 mmol) was added. The precipitated solid was collected by filtration and washed with diethyl ether, giving the dihydrochloride salt as a hygroscopic solid (150 mg). NMR: 1.17 (t, 3H), 2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.56 (q, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 4.38 (d, 1H), 4.49 (s, 2H), 6.88 (d, 2H), 7.23 (t, 1H), 7.32 (d, 2H), 7.37 (dd, 2H), 7.53 (d, 2H), 8.01 (s, 1H), 9.70 (br s, 1H), 9.97 (br s, 1H), 10.66 (s, 1H).

Example 87

4-Anilino-5-(hydroxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine dihydrochloride (Example 86; 50 mg, 0.11 mmol) was dissolved in water (3 ml) and the solution was heated under reflux for 3 hours. Volatile material was removed by evaporation and the residue was triturated with diethyl

ether, giving the product as a hygroscopic dihydrochloride salt (35 mg, 75%). NMR: 2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 4.38 (d, 1H), 4.51 (s, 2H), 6.88 (d, 2H), 7.22 (t, 1H), 7.32 (d, 2H), 7.37 (dd, 2H), 7.56 (d, 2H), 7.93 (s, 1H), 9.91 (s, 1H), 9.97 (br s, 1H), 10.55 (s, 1H); MS (MH^+): 410.3.

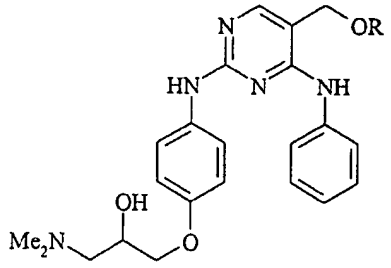
Example 88

4-Anilino-5-[(2-hydroxyethoxy)methyl]-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy] anilino}pyrimidine

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 86, 70 mg, 0.16 mmol) was dissolved in ethylene glycol (2 ml). Ethereal hydrogen chloride (1.0M; 0.32 ml, 0.32 mmol) was added, and the solution was heated at 100°C for 20 hours. Volatile material was removed by evaporation and the residue was triturated with diethyl ether, giving the product as a dihydrochloride salt (43 mg). NMR ($CDCl_3$): 2.34 (s, 6H), 2.3-2.6 (m, 2H), 3.63 (t, 2H), 3.73 (s, 1H), 3.86 (t, 2H), 3.96 (d, 2H), 4.08 (m, 1H), 4.54 (s, 2H), 6.86 (d, 2H), 6.88 (s, 1H), 7.08 (t, 1H), 7.30 (dd, 2H), 7.43 (d, 2H), 7.58 (d, 2H), 7.88 (m, 2H); MS (MH^+): 454.3.

Examples 89-92

The following compounds were prepared in by an analogous method to that described in Example 88, using 4-anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino) propoxy]anilino}pyrimidine (Example 86) and the appropriate alcohol.



Ex	R	NMR	MS (MH^+)
89	CH_2=$CHCH_2$-	2.80 (dd, 2H), 3.1-3.3 (m, 2H), 3.92 (m, 2H), 4.05 (d, 2H), 4.28 (m, 1H), 4.51 (s, 2H), 5.18 (d, 1H), 5.30 (dd, 1H), 5.95 (m, 1H), 6.86 (d, 2H), 7.22 (t, 1H), 7.32 (d, 2H), 7.39 (dd, 2H), 7.52 (d, 2H), 8.01 (s, 1H), 9.60 (s, 1H), 9.93 (br s, 1H), 10.53 (s, 1H)	450.4
90[1]	$PhCH_2$-	2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 4.60 (s, 4H), 6.87 (d, 2H), 7.20-7.45 (m, 10H), 7.56 (d, 2H), 8.04 (s, 1H), 9.69 (s, 1H), 9.87 (br s, 1H), 10.54 (s, 1H)	500.3
91	cyclohexyl	1.1-1.35 (m, 4H), 1.4-1.75 (m, 4H), 1.85-1.95 (m, 2H), 2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.45 (m, 1H), 3.94 (m, 2H), 4.28 (m, 1H), 4.54 (s, 2H), 6.89 (d, 2H), 7.21 (t, 1H), 7.36 (d, 2H), 7.37 (dd, 2H), 7.55 (d, 2H), 8.00 (s, 1H), 9.50 (s, 1H), 9.90 (br s, 1H), 10.52 (s, 1H)	492.5
92[1]	$HO(CH_2)_4$-	1.46 (m, 2H), 1.57 (m, 2H), 2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.40 (t, 2H), 3.50 (t, 2H), 3.95 (m, 2H), 4.28 (m, 1H), 4.58 (s, 2H), 6.88 (d, 2H), 7.23 (t, 1H), 7.35 (d, 2H), 7.38 (dd, 2H), 7.52 (d, 2H), 8.00 (s, 1H), 9.79 (s, 1H), 9.91 (br s, 1H), 10.54 (s, 1H)	482.3

[1]Diethyl ether was added to the cooled reaction mixture, followed by ethanol until the mixture was homogeneous. The supernatant liquor was decanted off, and the oily residue triturated with ether to give the solid product.

Example 93

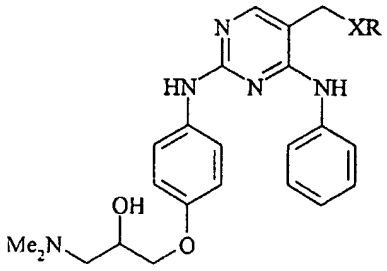
4-Anilino-5-[(5-methylisoxazol-3-yl)oxymethyl]-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino) propoxy]anilino}pyrimidine

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 86, 100 mg, 0.23 mmol) was dissolved in NMP (2 ml). 3-Hydroxy-5-methylisoxazole (45 mg, 0.46 mmol) and ethereal hydrogen chloride (1.0M; 0.46 ml, 0.46 mmol) were added, and the solution was heated at

100°C for 20 hours. Volatile material was removed by evaporation, and the residue was dissolved in 10% methanol solution in DCM (3 ml) and loaded on a Varian Mega Bond Elut column. The column was eluted with 0-2.5% methanol solution in DCM containing 0.5% aqueous ammonia solution. Concentration of the appropriate fractions and trituration of the residue with diethyl ether gave the product as a white crystalline solid (49 mg, 44%). NMR: 2.17 (s, 6H), 2.22 (s, 3H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.73 (br s, 1H), 4.99 (s, 2H), 5.78 (s, 1H), 6.80 (d, 2H), 7.02 (t, 1H), 7.30 (dd, 2H), 7.50 (d, 2H), 7.70 (d, 2H), 8.04 (s, 1H), 8.76 (s, 1H), 9.05 (s, 1H); MS (MH'): 491.5.

Examples 94-100

The following compounds were prepared by an analogous method to that described in Example 93 using 4-anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-*N,N*-dimethylamino) propoxy]anilino}pyrimidine (Example 86) and the appropriate heterocycle.



Ex	X	R	NMR	MS (MH^+)
94	O	isoxazol-3-yl	2.20 (s, 6H), 2.25-2.5 (m, 2H), 3.75-3.9 (m, 3H), 4.79 (br s, 1H), 5.06 (s, 2H), 6.05 (d, 1H), 6.80 (d, 2H), 7.02 (t, 1H), 7.29 (dd, 2H), 7.50 (d, 2H), 7.70 (d, 2H), 8.05 (s, 1H), 8.54 (d, 1H), 8.73 (s, 1H), 9.07 (s, 1H)	477.4
95[1]	NH	quinolin-6-yl	2.81 (dd, 2H), 3.1-3.3 (m, 2H), 3.94 (m, 2H), 4.28 (m, 1H), 4.57 (s, 2H), 6.00 (br s, 1H), 6.86 (d, 2H), 7.13 (s, 1H), 7.28 (t, 1H), 7.35 (d, 2H), 7.42 (dd, 2H), 7.60 (d, 2H), 7.66 (d, 2H), 7.82 (dd, 1H), 8.06 (s, 1H), 8.17 (d, 1H), 8.73 (d, 1H), 8.80 (d, 1H), 9.91 (br s, 1H), 10.12 (s, 1H)	536.4
96	NH	benzothien-6-yl	2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.27 (d, 2H), 4.80 (br s, 1H), 6.38 (t, 1H), 6.76 (d, 2H), 6.83 (d, 1H), 6.95 (d, 1H), 7.06 (t, 1H), 7.24 (s, 1H), 7.32 (dd, 2H), 7.53 (d, 2H), 7.67 (d, 2H), 7.72 (d, 1H), 7.78 (d, 1H), 8.04 (s, 1H), 8.38 (s, 1H), 8.93 (s, 1H)	542.3
97	NH	pyrazol-3-yl	2.18 (s, 6H), 2.2-2.4 (m, 2H), 3.75-3.9 (m, 3H), 4.18 (d, 2H), 4.72 (d, 1H), 5.50 (d, 1H), 5.68 (t, 1H), 6.78 (d, 2H), 7.00 (t, 1H), 7.27 (dd, 2H), 7.54 (d, 2H), 7.66 (d, 2H), 7.94 (s, 1H), 11.58 (d, 1H), 11.72 (s, 1H)	475.4
98[2]	NH	isoxazol-3-yl	2.81 (dd, 2H), 3.2-3.35 (m, 2H), 3.94 (m, 2H), 4.32 (m, 3H), 6.20 (d, 1H), 6.87 (d, 2H), 7.25 (t, 1H), 7.34 (d, 2H), 7.39 (dd, 2H), 7.60 (d, 2H), 7.95 (s, 1H), 8.45 (s, 1H), 9.85 (br s, 1H), 10.00 (s, 1H), 10.51 (s, 1H)	476.2
99	S	thiazol-2-yl	2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.74 (d, 1H), 5.32 (s, 2H), 6.78 (d, 2H), 7.05 (t, 1H), 7.13 (d, 1H), 7.31 (dd, 2H), 7.50 (d, 2H), 7.64 (d, 1H), 7.67 (d, 2H), 8.13 (s, 1H), 8.63 (d, 1H), 9.09 (s, 1H)	509.2

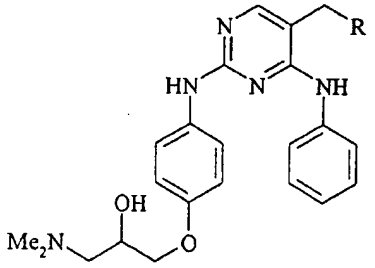
100	S	tetrazol-5-yl	2.76 (s, 6H), 3.1-3.4 (m, 2H), 3.90 (m, 2H), 4.20 (m, 1H), 4.28 (s, 2H), 5. 85 (br s, 1H), 6.80 (d, 2H), 7.20 (t, 1H), 7.29 (dd, 2H), 7.58 (d, 2H), 7.83 (d, 2H), 7.97 (s, 1H), 8.95 (s, 1H), 10.36 (s, 1H)	494.2

[1] Product isolated as trihydrochloride salt by filtration of the precipitate from cooled reaction mixture.

[2] Product isolated as dihydrochloride salt by evaporation of the reaction mixture and recrystallization of the residue twice from methanol/ether.

Examples 101-103

The following compounds were prepared by an analogous method to that described in Example 93, using 4-anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-*N,N*-dimethylamino) propoxy]anilino}pyrimidine (Example 86) and the appropriate amine hydrochloride salt.



Ex	R	NMR ($CDCl_3$)	MS (MH^+)
101[1]	Me_2N-	2.29 (s, 6H), 2.3-2.6 (m, 2H), 2.33 (s, 6H), 3.37 (s, 2H), 3.97 (d, 2H), 4.08 (m, 1H), 6.80 (s, 1H), 6.88 (d, 2H), 7.02 (t, 1H), 7.30 (dd, 2H), 7.46 (d, 2H), 7.57 (d, 2H), 7.78 (s, 1H), 9.88 (s, 1H)	437.4
102[2]	Et_2N-	1.12 (t, 6H), 2.33 (s, 6H), 2.3-2.6 (m, 2H), 2.59 (q, 4H), 3.51 (s, 2H), 3.97 (d, 2H), 4.07 (m, 1H), 6.78 (s, 1H), 6.88 (d, 2H), 7.02 (t, 1H), 7.30 (dd, 2H), 7.46 (d, 2H), 7.58 (d, 2H), 7.78 (s, 1H), 10.28 (s, 1H)	465.5

103[3]	MeNH-	2.3-2.6 (m, 2H), 2.33 (s, 6H), 2.48 (s, 3H), 2.59 (t, 1H), 3.72 (s, 2H), 3.97 (d, 2H), 4.08 (m, 1H), 4.56 (s, 1H), 6.86 (s, 1H), 6.87 (d, 2H), 7.02 (t, 1H), 7.30 (dd, 2H), 7.45 (d, 2H), 7.58 (d, 2H), 7.80 (s, 1H), 9.92 (s, 1H)	423.4

[1] Reaction performed at 160°C for 4 hours with DMF as solvent.

[2] Reaction performed at 160°C for 3 hours.

[3] Reaction performed at 120°C for 2 hours.

Example 104

4-Anilino-5-(formamido)methyl-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 86, 70 mg, 0.16 mmol) was dissolved in formamide (5 ml). Ethereal hydrogen chloride (1.0M; 0.19 ml, 0.19 mmol) was added, and the mixture was heated on power level 2 in a Toshiba Deltawave III domestic microwave oven (650W) for 90 seconds. Excess formamide was removed by vacuum distillation and the residue was triturated with ethanol and diethyl ether, giving the product as a hygroscopic dihydrochloride salt (20 mg, 24%). NMR: 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.21 (d, 2H), 4.76 (br d, 1H), 6.79 (d, 2H), 7.01 (t, 1H), 7.29 (dd, 2H), 7.52 (d, 2H), 7.71 (d, 2H), 7.92 (s, 1H), 8.13 (d, 1H), 8.69 (t, 1H), 8.92 (s, 1H), 8.94 (s, 1H); MS (MH^+): 437.4.

Example 105

4-Anilino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-5-ureidomethyl-pyrimidine

4-Anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 86, 70 mg, 0.16 mmol) was dissolved in 1,4-dioxane (2 ml). Urea (12 mg, 0.19 mmol) and ethereal hydrogen chloride (1.0M; 0.19ml, 0.19 mmol) were added, and the suspension was heated at 100°C for 20 hours. Diethyl ether (20 ml) was added, and the precipitated solid collected by filtration. The solid was dissolved in 10% methanol solution in DCM (3 ml), and loaded on a Varian Mega Bond Elut column. The column was eluted with 0-2.5% methanol solution in DCM containing 0.5%

aqueous ammonia solution. Concentration of the appropriate fractions and trituration of the residue with diethyl ether gave the product as a white crystalline solid (20 mg, 28%). NMR: 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.07 (d, 2H), 4.74 (br d, 1H), 5.85 (s, 2H), 6.62 (t, 1H), 6.80 (d, 2H), 6.98 (t, 1H), 7.27 (dd, 2H), 7.54 (d, 2H), 7.77 (d, 2H), 7.88 (s, 1H), 8.88 (s, 1H), 9.88 (s, 1H); MS (MH^+): 452.4.

Example 106

4-Anilino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-5-(imidazol-1-ylmethyl) pyrimidine

Using an analogous method to that described in Example 105, but starting from 4-anilino-5-(ethoxymethyl)-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 86) and imidazole, the product was obtained in 25% yield. NMR: 2.18 (s, 6H), 2.2-2.45 (m, 2H), 3.75-3.9 (m, 3H), 4.76 (br s, 1H), 5.20 (s, 2H), 6.75 (d, 2H), 6.89 (d, 1H), 7.08 (t, 1H), 7.20 (d, 1H), 7.32 (dd, 2H), 7.50 (d, 2H), 7.61 (d, 2H), 7.78 (s, 1H), 7.96 (s, 1H), 8.54 (s, 1H), 9.00 (s, 1H); MS (MH^+): 460.4.

Example 107

4-Anilino-5-carboxy-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}pyrimidine

4-Anilino-5-ethoxycarbonyl-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Method 1; 200 mg, 0.44 mmol) was suspended in ethanol (5 ml) and concentrated hydrochloric acid (2 ml), and the mixture was heated at 100°C for 24 hours. Volatile material was removed by evaporation and the residue was triturated with isopropanol to give the product as a hydrochloride salt (50 mg, 25%). NMR: 2.8 (s, 6H), 3.2 (m, 2H), 3.9 (m, 2H), 4.2 (m, 1H), 6.9 (d, 2H), 7.1 (d, 2H), 7.15 (t, 1H) 7.3-7.7 (m, 8H), 8.7 (s, 1H), 10.0 (s, 1H), 10.55 (s, 1H); MS (MH^-): 424.

Example 108

5-Amino-4-anilino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}pyrimidine

4-Anilino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-5-nitropyrimidine (Example 20, 400 mg, 0.90 mmol) was dissolved in ethanol (20 ml). Under an atmosphere of nitrogen, cyclohexene (5 ml) was added followed by 10% palladium-on-

carbon (100 mg). The mixture was heated under reflux for 5 hours, and then a further portion of 10% palladium on carbon (100 mg) was added and heating was continued for 18 hours. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated by evaporation. The resulting oil was purified by column chromatography, eluting with 0-10% 2.0M methanolic ammonia in DCM to give the product as a white solid (300 mg, 80%). NMR: 2.15 (s, 6H), 2.3 (m, 2H), 3.8 (m, 3H), 4.3 (s, 2H), 4. 7 (s, 1H), 6.8 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.5 (d, 2H), 7.6 (s, 1H), 7.8 (d, 2H), 8.1 (s, 1H), 8.4 (s, 1H); MS (MH^+): 395.

Example 109

4-Anilino-5-benzamido-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}pyrimidine

5-Amino-4-anilino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine (Example 108; 100 mg, 0.25 mmol) and benzoic acid (30 mg, 0.25 mmol) were dissolved in DMF (3 ml). 4-*N,N*-dimethylaminopyridine (90 mg, 0.74 mmol) and 1-(3-*N,N*-dimethylaminopropyl-3-ethylcarbodiimide) hydrochloride (72 mg, 0.38 mmol) were added and the solution was stirred overnight. Silica (1 g) was added and volatile material was removed by evaporation. The residue was purified by column chromatography, eluting with 0-10% 2M methanolic ammonia in DCM. Concentration of the appropriate fractions gave the product as a solid (25 mg, 20%). NMR: 2.2 (s, 6H), 2.4 (m, 2H), 3.9 (m, 3H), 6.8 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.55 (m, 5H), 7.65 (d, 2H), 7.95 (s, 1H), 8.05 (d, 2H), 8.6 (s, 1H), 9.0 (s, 1H), 8.6 (s, 1H); MS (MH^+): 499.

Example 110

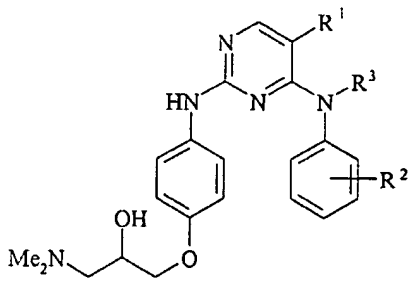
Chiral separation of 4-anilino-5-bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy] anilino}pyrimidine

Racemic 4-anilino-5-bromo-2-{4-[3-(*N,N*-dimethyl)amino-2-hydroxypropoxy]anilino} pyrimidine (Example 3; 200 mg) was applied to a Chiralcel OJ column (Daicel Technologies Ltd; 250 cm x 2 cm), mobile phase iso-hexane/isopropanol/triethylamine (60:40:0.1, flow rate 9 ml/min). The resolved enantiomers were isolated and the solvent was removed. Enantiomeric purities were determined using a Chiralcel OJ column (250 mm x 4.6 mm), mobile phase isohexane/isopropanol/triethylamine (70:30:0.1, flow 1 ml/min, wavelength 254

nm). First eluted enantiomer (66 mg): retention time 23.27 minutes (analytical), 35 minutes (preparative). Second eluted enantiomer (67 mg): retention time 28.85 minutes (analytical), 43 minutes (preparative).

Examples 111-117

The following compounds were prepared by an analogous method to that described in Example 1 using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89) and the appropriate 4-anilino-2-chloro-5-halopyrimidine intermediate (Methods 74-80).

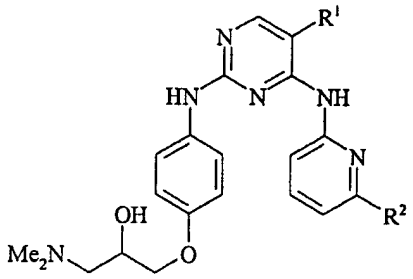


Ex	R^1	R^2	R^3	NMR (373K)	MS (MH^+)
111	Br	H	$-(CH_2)_3CF_3$	1.81 (m, 2H), 2.21 (m, 2H), 2.29 (s, 6H), 2.49 (m, 2H), 3.95 (m, 5H), 6.88 (d, 2H), 7.13 (d, 2H), 7.19 (t, 1H), 7.36 (t, 2H), 7.48 (d, 2H), 8.08 (s, 1H), 8.81 (s, 1H)	568.5, 570.1
112	Cl	H	$-(CH_2)_3CF_3$	1.84 (m, 2H), 2.21 (m, 8H), 2.35 (m, 1H), 2.41 (dd, 1H), 3.92 (m, 5H), 4.30 (bs, 1H), 6.87 (d, 2H), 7.15 (d, 2H), 7.20 (t, 1H), 7.36 (t, 2H), 7.48 (d, 2H), 7.95 (s, 1H), 8.78 (s, 1H)	524.4, 526.4

113	Cl	4-Br	$-(CH_2)_3CF_3$	1.81 (m, 2H), 2.21 (m, 8H), 2.34 (m, 1H), 2.41 (dd, 1H), 3.91 (m, 5H), 4.29 (bs, 1H), 6.86 (d, 2H), 7.11 (d, 2H), 7.47 (d, 2H), 7.51 (d, 2H), 8.00 (s, 1H), 8.85 (s, 1H)	602.4, 604.4, 606.4
114	Cl	4-Br	$-CH_2CH=CHBr$	2.21 (s, 6H), 2.38 (m, 1H), 2.44 (dd, 1H), 3.90 (m, 3H), 4.30 (bs, 1H), 4.50 (s, 1H), 4.64 (s, 1H), 6.39 (s, 1H), 6.49 (s, 1H), 6.86 (t, 2H), 7.10 (q, 2H), 7.50 (m, 4H), 8.02 (s, 1H), 8.90 (s, 1H)	610.3, 612.3, 614.3
115	Cl	2-F, 5-Me	$-CH_2CH=CHPh$	2.20 (s, 6H), 2.26 (s, 3H), 2.32 (m, 1H), 2.40 (dd, 1H), 3.85 (m, 3H), 4.29 (bs, 1H), 4.64 (d, 2H), 6.37 (m, 1H), 6.45 (d, 1H), 6.82 (d, 2H), 7.08 (d, 2H), 7.19 (m, 2H), 7.26 (d, 4H), 7.50 (d, 2H), 7.96 (s, 1H), 8.85 (bs, 1H)	562.5, 564.5
116	Cl	H	Me	(293K) 2.15 (s, 6H), 2.3 (m, 2H), 3.4 (s, 3H), 3.9 (m, 3H), 4.7 (d, 1H), 6.85 (d, 2H), 7.2 (m, 3H), 7.4 (t, 2H), 7.6 (d, 2H), 8.0 (s, 1H), 9.3 (s, 1H)	428, 430
117	Br	H	Me	(293K) 2.2 (s, 6H), 2.3 (m, 2H), 3.4 (s, 3H), 3.85 (m, 3H), 4.8 (d, 1H), 6.8 (d, 2H), 7.2 (m, 3H), 7.35 (t, 2H), 7.6 (d, 2H), 8.1 (s, 1H), 9.4 (s, 1H)[2]	472, 474

Examples 118-120

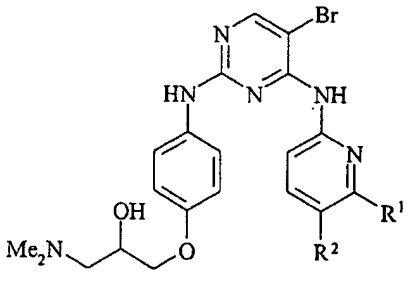
The following compounds were prepared by an analogous method to that described in Example 1 using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89) and the appropriate 2-chloro-5-halo-4-(2-pyridylamino) pyrimidine intermediate (Methods 81-83).



Ex	R^1	R^2	NMR	MS (MH^+)
118	Br	H	2.1 (s, 6H), 2.5 (m, 2H), 3.7-4.0 (m, 3H), 4.8 (s, 1H), 6.9 (d, 2H), 7.1 (t, 1H), 7.5 (t, 1H), 8.1-8.4 (m, 4H), 9.3 (s, 1H)	459, 461
119	Cl	Me	2.2 (s, 6H), 2.3 (m, 2H), 2.4 (s, 3H), 3.9 (m, 3H), 4.8 (d, 1H), 6.9 (d, 2H), 7.0 (d, 1H), 7.5 (d, 2H), 7.6 (t, 1H), 8.0 (m, 1H), 8.2 (s, 1H), 8.3 (s, 1H), 9.3 (s, 1H)	429, 431
120	Cl	H	2.2 (s, 6H), 2.3 (m, 2H), 3.9 (m, 3H), 4.8 (d, 1H), 6.8 (d, 2H), 7.1 (m, 1H), 7.5 (d, 2H), 7.8 (m, 1H), 8.2 (m, 2H), 8.35 (d, 1H), 8.45 (s, 1H), 9.3 (s, 1H)	415, 417

Examples 121-124

The following compounds were prepared by an analogous method to that described in Example 44 using 5-bromo-2,4-dichloropyrimidine, the appropriate substituted 2-aminopyridine and 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89).

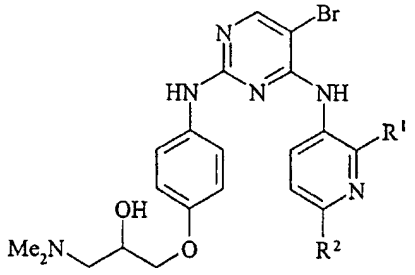


Ex	R^1	R^2	NMR	MS (MH^+)
121[1]	H	Br	2.8 (s, 6H), 3.3 (m, 2H), 3.95 (m, 2H), 4.2 (m, 1H), 6.9 (d, 2H), 7.5 (d, 2H), 7.9 (m, 1H), 8.2 (m, 3H), 8.4 (s, 1H)[2]	538, 540, 542
122	H	Cl	(CD_3CO_2D) 2.8 (s, 6H), 3.3 (m, 2H), 3.95 (m, 2H), 4.3 (m, 1H), 6.9 (d, 2H), 7.5 (d, 2H), 7.8 (d, 1H), 8.3 (m, 2H), 8.4 (s, 1H)	493, 495, 497
123	H	Me	2.3 (s, 3H), 2.8 (s, 6H), 3.2 (m, 2H), 3.9 (m, 2H), 4.25 (m, 1H), 5.85 (s, 1H), 6.9 (d, 2H), 7.5 (d, 2H), 7.6 (d, 1H), 8.1 (m, 2H), 8.2 (s, 1H), 8.25 (s, 1H), 9.3 (s, 1H)	473, 475
124	Me	H	2.35 (s, 6H), 2.4 (s, 3H), 2.6 (m, 2H), 3.8-4.0 (m, 3H), 6.8 (d, 2H), 7.0 (d, 1H), 7.5 (d, 2H), 7.7 (t, 1H), 8.0 (m, 2H), 8.3 (s, 1H), 9.3 (s, 1H)	473, 475

[1] Isolated as a hydrochloride salt

Examples 125-126

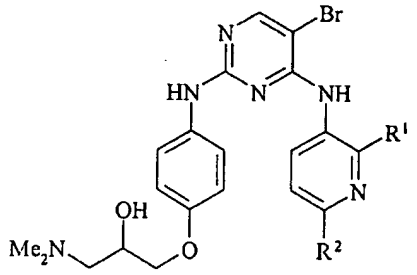
The following compounds were prepared by an analogous method to that described in Example 1, using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride (Method 89) and the appropriate 5-bromo-2-chloro-4-(3-pyridylamino)pyrimidine intermediate (Methods 85-86).



Ex	R^1	R^2	NMR	MS (MH^+)
125	NH_2	H	2.15 (s, 6H), 2.3 (m, 2H), 3.7 (m, 1H), 3.9 (m, 2H), 4.7 (s, 1H), 5.6 (s, 2H), 6.6 (m, 3H), 7.4 (m, 3H), 7.9 (d, 1H), 8.1 (d, 2H), 9.0 (s, 1H)	474, 476
126	H	MeO-	2.2 (s, 6H), 2.3 (m, 2H), 3.9 (m, 1H), 3.85 (m, 5H), 4.8 (s, 1H), 6.7 (d, 2H), 6.8 (d, 1H), 7.4 (d, 2H), 7.8 (m, 1H), 8.1 (s, 1H), 8.3 (s, 1H), 8.6 (s, 1H), 9.1 (s, 1H)	489, 491

Examples 127-132

The following compounds were prepared by an analogous method to that described in Example 44 using 5-bromo-2,4-dichloropyrimidine, the appropriate substituted 3-aminopyridine and 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride.



Ex	R^1	R^2	NMR	MS (MH^+)
127[1]	H	Cl	2.6 (s, 6H), 2.9 (m, 2H), 3.9 (m, 2H), 4.15 (m, 1H), 6.8 (d, 2H), 7.45 (m, 3), 8.1 (m, 1H), 8.2 (s, 1H), 8.7 (s, 1H), 8.85 (s, 1H), 9.15 (s, 1H)	493, 495, 497
128[1]	Cl	H	2.8 (s, 6H), 3.2 (m, 2H), 3.85 (m, 2H), 4.2 (m, 1H), 5.9 (s, 1H), 6.7 (d, 2H), 7.3 (d, 2H), 7.5 (m, 1H), 8.2 (m, 2H), 8.3 (m, 1H), 8.6 (s, 1H), 9.3 (s, 1H)	493, 495, 497
129	MeO-	MeO-	2.4 (s, 6H), 2.6 (m, 2H), 3.7-3.8 (m, 8H), 4.0 (m, 1H), 6.4 (d, 1H), 6.7 (d, 2H), 7.4 (d, 2H), 7.9 (d, 1H), 8.0 (s, 1H), 8.1 (s, 1H), 9.1 (s, 1H)	519, 521

130	Me	Me	2.3 (s, 3H), 2.5 (s, 3H), 2.7 (s, 6H), 3.0 (m, 2H), 3.8 (m, 2H), 4.2 (m, 1H), 5.7 (s, 1H), 6.6 (d, 2H), 7.1 (d, 1H), 7.3 (d, 2H), 7.6 (d, 1H), 8.1 (s, 1H), 8.5 (s, 1H), 9.05 (s, 1H)	487, 489
131	H	Me	2.3 (s, 6H), 2.35-2.5 (5H), 3.8 (m, 1H), 3.9 (m, 2H), 6.7 (d, 2H), 7.2 (d, 1H), 7.4 (d, 2H), 7.9 (m, 1H), 8.15 (s, 1H), 8.6 (s, 2H), 9.1 (s, 1H)	473, 475
132	H	Br	2.2 (s, 6H), 2.4 (m, 2H), 3.8 (m, 1H), 3.9 (m, 2H), 4.8 (s, 1H), 6.6 (d, 2H), 7.4 (d, 2H), 7.6 (d, 1H), 8.1 (m, 1H), 8.2 (s, 1H), 8.7 (s, 1H), 8.8 (s, 1H), 9.2 (s, 1H)	539, 541

[1] Isolated as a hydrochloride salt.

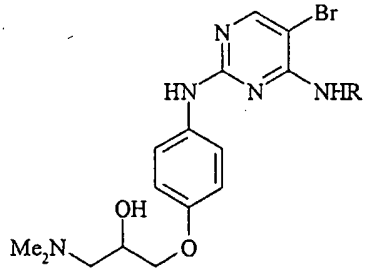
Example 133

5-Bromo-4-(2-bromo-6-methylpyrid-4-yl)amino-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino) propoxy]anilino}pyrimidine

Using an analogous method to that described in Example 44, but starting from 4-amino-2-bromo-6-methylpyridine, the product was obtained. NMR: 2.3 (s, 3H), 2.8 (s, 6H), 3.2 (m, 2H), 3.8 (m, 3H), 5.8 (m, 1H), 6.9 (d, 2H), 7.2 (s, 1H), 7.5 (d, 2H), 7.8 (s, 1H), 8.3 (s, 1H), 9.5 (s, 1H); MS (MH^+): 551, 553, 555.

Examples 134-135

The following compounds were prepared by an analogous method to that described in Example 1 using 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride and the appropriate 4-substituted 5-bromo-2-chloropyrimidine intermediate (Methods 87-88).



Ex	R	NMR	MS (MH^+)
134	4-methyl-thiazol-2-yl	2.2 (m, 9H), 2.3 (m, 2H), 3.9 (m, 3H), 4.8 (s, 1H), 6.6 (s, 1H), 6.9 (d, 2H), 7.5 (d, 2H), 8.2 (s, 1H), 9.0 (s, 1H)	479, 481
135	5-methyl-pyrazol-3-yl	2.1- 2.5 (m, 11H), 3.9 (m, 3H), 4.8 (s, 1H), 6.35 (s, 1H), 6.9 (m, 2H), 7.5 (d, 2H), 8.2 (m, 2H), 9.1 (s, 1H), 12.1 (s, 1H)	462, 464

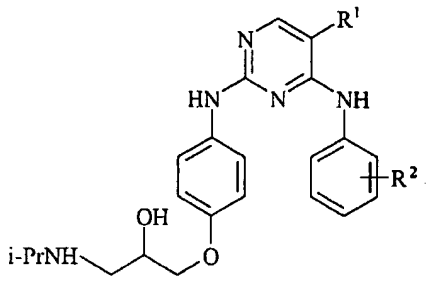
Example 136

4-Anilino-5-chloro-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]anilino}pyrimidine

4-Anilino-2,5-dichloropyrimidine (Method 7, 241 mg, 1.0 mmol) was dissolved in *n*-butanol (20 ml) and methanol (4 ml). 4-[2-Hydroxy-3-(isopropylamino)propoxy]aniline (obtained as described in Pharmazie 1980, 35, 278; 202 mg, 0.9 mmol) and ethereal hydrogen chloride (1.0M; 2 ml, 2.0 mmol) were added and the solution was heated at 100°C for 20 hours, allowed to cool to ambient temperature and then concentrated to a volume of 5 ml. The solution was loaded on a Varian Mega Bond Elut column and the column was eluted with 0-4% 2.0M methanolic ammonia solution in DCM. Concentration of the appropriate fractions and recrystallization of the residue from acetonitrile gave the product as a white solid (159 mg, 41%). NMR: 1.0 (d, 6H), 2.5-2.6 (m, 1H), 2.65-2.75 (m, 2H), 3.8-3.95 (m, 3H), 4.9 (br s, 1H), 6.8 (d, 2H), 7.1 (t, 1H), 7.35 (t, 2H), 7.45 (d, 2H), 7.65 (d, 2H), 8.1 (s, 1H), 8.7 (s, 1H), 9.1 (s, 1H); MS (MH^+): 428, 430.

Examples 137-150

The following compounds were prepared by an analogous method to that described in Example 136 using 4-[2-hydroxy-3-(isopropylamino)propoxy]aniline (Pharmazie 1980, 35, 278) and the appropriate 5-substituted 4-anilino-2-chloropyrimidine intermediate (Methods 12-13, 15, 20, 43, 49-56).



Ex	R^1	R^2	NMR/HPLC	MS (MH^+)
137	Br	H	RT: 2.87	472, 474
138	Br	2,4-di-F	1.3 (m, 6H), 2.9 (m, 1H), 3.1 (m, 1H), 3.3 (m, 1H), 3.9 (m, 2H), 4.2 (m, 1H), 6.7 (m, 2H), 7.1-7.3 (m, 3H), 7.5 (m, 2H), 8.3 (s, 1H), 8.6 (m, 1H), 8.9 (m, 1H), 9.3 (s, 1H), 9.9 (m, 1H)	508, 510
139	Br	3,4-$(CH_2)_3$-**	1.0 (m, 6H), 2.0 (m, 2H), 2.5-2.7 (m, 3H), 2.8 (m, 4H), 3.8 (m, 3H), 6.7 (m, 2H), 7.2 (m, 1H), 7.3 (m, 1H), 7.4 (m, 3H), 8.1 (s, 1H), 8.3 (s, 1H), 9.0 (s, 1H)	512, 514
140	Br	4-OMe	1.3 (m, 6H), 2.9 (m, 1H), 3.1 (m, 1H), 3.3 (m, 1H), 3.8 (s, 3H), 3.9 (m, 2H), 4.2 (m, 1H), 6.8 (m, 2H), 7.0 (m, 2H), 7.3-7.4 (m, 4H), 8.3 (s, 1H), 8.6 (m, 1H), 8.9 (m, 1H), 9.5 (s, 1H), 9.9 (m, 1H)	502, 504
141	Me	H	1.0 (d, 6H), 2.1 (s, 3H), 2.5-2.6 (m, 1H), 2.6-2.75 (m, 2H), 3.75-3.9 (m, 3H), 4.85 (br s, 1H), 6.95 (d, 2H), 7.0 (t, 1H), 7.3 (t, 2H), 7.55 (d, 2H), 7.7 (d, 2H), 7.8 (s, 1H), 8.2 (s, 1H), 8.7 (s, 1H)	408.2
142	Br	2-$HOCH_2$-	0.96 (d, 6H), 2.4-2.75 (m, 3H), 3.75-3.9 (m, 3H), 4.54 (s, 2H), 4.87 (br s, 1H), 5.64 (br s, 1H), 6.74 (d, 2H), 7.13 (dd, 1H), 7.30 (dd, 1H), 7.34 (d, 1H), 7.43 (d, 1H), 7.93 (d, 1H), 8.16 (s, 1H), 8.91 (br s, 1H), 9.11 (s, 1H)	502.2, 504.2

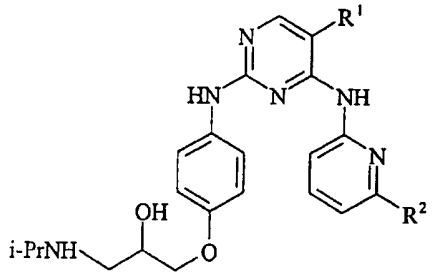
143	Br	4-$HOCH_2$-	0.97 (d, 6H), 1.50 (br s, 1H), 2.4-2.75 (m, 3H), 3.75-3.9 (m, 3H), 4.48 (s, 2H), 4.87 (br s, 1H), 5.14 (br s, 1H), 6.74 (d, 2H), 7.27 (d, 2H), 7.44 (d, 2H), 7.53 (d, 2H), 8.14 (s, 1H), 8.43 (s, 1H), 9.07 (s, 1H)	502.5, 504.5
144	Br	4-F	0.97 (d, 6H), 2.5-2.7 (m, 2H), 2.65-2.75 (m, 1H), 3.76-3.91 (m, 3H), 4.85 (br s, 1H), 6.74 (d, 2H), 7.17 (dd, 2H), 7.41 (d, 2H), 7.60 (dd, 2H), 8.14 (s, 1H), 8.53 (s, 1H), 9.08 (s, 1H)	490.1, 492.1
145[1]	CN	H	0.97 (d, 6H), 2.4-2.75 (m, 3H), 3.75-3.9 (m, 3H), 4.88 (br s, 1H), 6.76 (br d, 2H), 7.14 (t, 1H), 7.34 (dd, 2H), 7.44 (d, 2H), 7.55 (br d, 2H), 8.04 (s, 1H), 9.40 (br s, 1H), 9.71 (br s, 1H)	419.4
146	Br	3,4-di-F	RT: 4.07	508, 510
147	Br	3-Me	RT: 3.30	486, 488
148	Cl	4-F	0.97 (d, 6H), 2.5-2.7 (m, 2H), 2.65-2.75 (m, 1H), 3.76-3.91 (m, 3H), 4.85 (br s, 1H), 6.76 (d, 2H), 7.28 (dd, 2H), 7.43 (d, 2H), 7.64 (dd, 2H), 8.07 (s, 1H), 8.79 (s, 1H), 9.09 (s, 1H)	446, 448
149	Br	4-Br	RT: 4.68	551, 553
150	Br	3-F	RT: 3.20	490, 492

[1] Prepared from 4-anilino-5-cyano-2-(methanesulphonyl)pyrimidine (Method 64).

** Such that R^2 and the phenyl ring to which it is attached forms indan-5-yl.

Examples 151-154

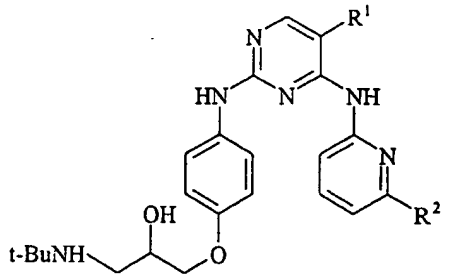
The following compounds were prepared by an analogous method to that described in Example 136 using 4-[2-hydroxy-3-(isopropylamino)propoxy]aniline (Pharmazic 1980, 35, 278) and the appropriate 2-chloro-5-halo-4-(2-pyridylamino)pyrimidine (Methods 81-84).



Ex	R^1	R^2	NMR	MS (MH^+)
151	Br	Me	0.9 (s, 3H), 0.95 (s, 3H), 2.4 (s, 3H), 2.55 (m, 1H), 2.8 (m, 2H), 3.8 (m, 3H), 4.95 (s, 1H), 6.9 (d, 2H), 7.0 (d, 1H), 7.5 (d, 2H), 2.7 (t, 1H), 8.1 (s, 2H), 8.3 (s, 1H), 9.3 (s, 1H)	487, 489
152	Br	H	0.9 (s, 3H), 0.95 (s, 3H), 2.5 (m, 1H), 2.7 (m, 2H), 3.9 (m, 3H), 4.9 (s, 1H), 6.8 (d, 2H), 7.1 (t, 1H), 7.5 (d, 2H), 7.8 (t, 1H), 8.2 (s, 2H), 8.3 (s, 1H), 8.35 (d, 1H), 9.4 (s, 1H)	473, 475
153	Cl	H	0.95 (s, 3H), 1.0 (s, 3H), 2.5 (m, 1H), 2.7 (m, 2H), 3.8 (m, 3H), 4.9 (s, 1H), 6.85 (d, 2H), 7.1 (t, 1H), 7.5 (d, 2H), 7.8 (t, 1H), 8.2 (m, 2H), 8.35 (d, 1H), 9.3 (s, 1H)	429, 431
154	Cl	Me	0.95 (s, 3H), 1.0 (s, 3H), 2.4 (s, 3H), 2.55 (m, 1H), 2.7 (m, 2H), 3.8 (m, 3H), 4.9 (s, 1H), 6.8 (d, 2H), 7.0 (d, 1H), 7.5 (d, 2H), 7.65 (t, 1H), 8.0 (m, 1H), 8.2 (s, 1H), 9.3 (s, 1H)	443, 445

Examples 155-158

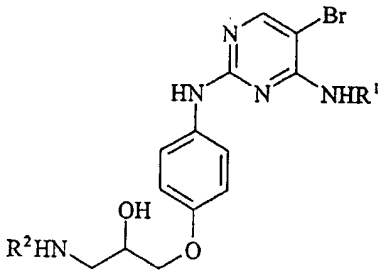
The following compounds were prepared by an analogous method to that described in Example 136 using 4-[3-(*t*-butylamino)-2-hydroxypropoxy]aniline (obtained as described in Pharmazie, 1980, 35, 278) and the appropriate 2-chloro-5-halo-4-(2-pyridylamino) pyrimidine intermediate.



Ex	R^1	R^2	NMR	MS (MH^+)
155	Br	H	0.9 (s, 9H), 2.5 (m, 2H), 3.8 (m, 3H), 4.8 (s, 1H), 6.9 (d, 2H), 7.1 (t, 1H), 7.5 (d, 2H), 7.8 (t, 1H), 8.2 (m, 2H), 8.3 (s, 1H), 8.4 (d, 1H), 9.3 (s, 1H)	487, 489
156	Br	Me	1.1 (s, 9H), 2.4 (s, 3H), 2.7 m, 1H), 2.9 (m, 1H), 3.9 (m, 3H), 6.9 (d, 2H), 7.0 (d, 1H), 7.5 (d, 2H), 7.65 (t, 1H), 8.0 (m, 2H), 8.25 (s, 1H), 9.3 (s, 1H)	501, 503
157	Cl	H	1.0 (s, 9H), 2.6 (m, 2H), 3.8 (m, 3H), 4.8 (s, 1H), 6.8 (d, 2H), 7.1 (t, 1H), 7.6 (d, 2H), 7.8 (t, 1H), 8.1 (m, 2H), 8.3 (d, 1H), 9.3 (s, 1H)	443, 445
158	Cl	Me	1.1 (s, 9H), 2.4 (s, 3H), 2.6 (m, 2H), 3.9 (m, 3H), 4. 9 (s, 1H), 6.8 (d, 2H), 7.0 (d, 2H), 7.5 (d, 2H), 7.65 (t, 1H), 8.0 (d, 1H), 8.2 (s, 1H), 9.3 (s, 1H)	457, 459

Examples 159-161

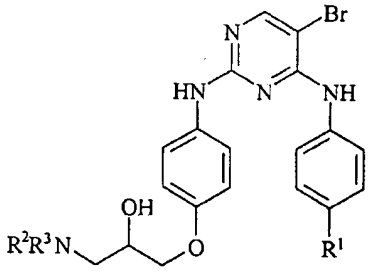
The following compounds were prepared by an analogous method to that described in Example 136, using the appropriate substituted aniline and the appropriate 4-substituted 5-bromo-2-chloropyrimidine intermediate.



Ex	R^1	R^2	NMR	MS (MH^+)
159	4-methyl-thiazol-2-yl	*i*-Pr	0.95 (s, 3H), 1.0 (s, 3H), 2.2 (s, 3H), 2.55 (m, 1H), 2.7 (m, 2H), 3.9 (m, 3H), 6.6 (s, 1H), 6.9 (d, 2H), 7.5 (d, 2H), 8.2 (s, 1H), 9.0 (s, 1H)	493, 495
160	5-methyl-pyrazol-3-yl	*i*-Pr	0.95 (s, 3H), 1.0 (s, 3H), 2.2 (s, 3H), 2.55 (m, 1H), 2.7 (m, 2H), 3.8 (m, 3H), 4.9 (s, 1H), 6.35 (s, 1H), 6.8 (d, 2H), 7.5 (d, 2H), 8.2 (m, 2H), 9.1 (s, 1H), 12.1 (s, 1H)	476, 478
161	5-methyl-pyrazol-3-yl	*t*-Bu	1.0 (s, 9H), 2.2 (s, 3H), 2.6 (m, 2H), 3.9 (m, 3H), 6.3 (s, 1H), 6.8 (d, 2H), 7.5 (d, 2H), 8.1 (s, 1H), 8.2 (s, 1H), 9.1 (s, 1H), 12.1 (1H)	490, 492

Examples 162-178

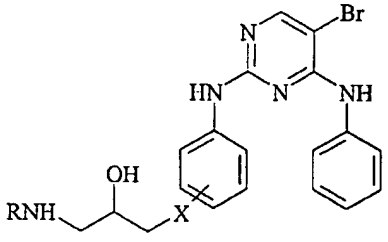
The following compounds were prepared by an analogous method to that described in Example 136, using the appropriate substituted aniline (Methods 91-101) and the appropriate 4-anilino-5-bromo-2-chloropyrimidine.



Ex	R^1	R^2	R^3	MS (MH^+)	HPLC (RT)
162	H	$PhCH_2$-	*i*-Pr	562, 564	6.25
163	MeO-	CH_2=$CHCH_2$-	Me	514, 516	3.06
164	MeO-	*i*-Bu	H	516, 518	3.33
165	MeO-	cyclopentyl	H	529, 531	3.48
166	MeO-	pyrrolidino		515, 517	3.76
167	H	cyclopentyl	H	499, 501	3.57
168	H	*i*-Bu	H	486, 488	4.10
169	MeO-	Me	H	474, 476	3.00
170	H	pyrrolidino		485, 487	3.89
171	H	Me	H	444, 446	2.70
172	H	H	H	430, 432	2.33
173	MeO-	H	H	460, 462	3.59
174	H	Et	H	458, 460	2.99
175	MeO-	Et	H	488, 490	3.17
176	H	morpholino		500, 502	2.89
177	H	4-acetylpiperazin-1-yl		541, 543	2.88
178	MeO-	4-methylpiperazin-1-yl		543, 545	2.18

Examples 179-180

The following compounds were prepared by an analogous method to that described in Example 136, using the appropriate substituted aniline (obtained as described in Pharmazie, 1980, 35, 278) and 4-anilino-5-bromo-2-chloropyrimidine (Method 13).



Ex	X	R	MS (MH^+)	HPLC (RT)
179	3-O	*i*-Pr	472, 474	4.19
180	4-O	*t*-Bu	486, 488	4.38

Example 181

4-Anilino-5-bromo-2-{4-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]anilino}pyrimidine

A mixture of potassium carbonate (160 mg, 1.1 mmol), epibromohydrin (0.14 ml, 1.7 mmol) and 4-anilino-5-bromo-2-(4-hydroxyanilino)pyrimidine (Method 4, 200 mg, 0.56 mmol) in DMSO (2 ml) was stirred for 12 hours. 1-Methylpiperazine (0.62 ml) was added dropwise and the resulting solution was stirred for a further 12 hours. Silica (1 g) was added and volatile material was removed by evaporation. The residue was loaded onto a Varian Mega Bond Elut column and the column was eluted with 50:50 iso-hexane : DCM (2 x 20 ml), DCM (2 x 20 ml), 2% 2M NH_3/MeOH/DCM (2 x 20 ml), 4% 2M NH_3/MeOH/DCM (2 x 20 ml), 6% 2M NH_3/MeOH/DCM (2 x 20 ml) and 10% 2M NH_3/MeOH/DCM (8 x 20 ml). Concentration of the appropriate fractions gave the product as a yellow gum (87 mg, 30%). MS (MH^+): 513, 515; HPLC (RT): 1.85.

Example 182

4-Anilino-5-bromo-2-{3-[2-hydroxy-3-(4-methylpiperazin-1-yl)propoxy]anilino}pyrimidine

Using an analogous procedure to that described in Example 181, but starting from 4-anilino-5-bromo-2-(3-hydroxyanilino)pyrimidine (Method 6), the title product was obtained. MS (MH^+): 513, 515; HPLC (RT): 2.00.

Example 183

4-Anilino-5-bromo-2-{4-[3-(4-methylpiperazin-1-yl)propoxy]anilino}pyrimidine

A mixture of potassium carbonate (180 mg, 1.3 mmol), 4-anilino-5-bromo-2-(4-hydroxyanilino)pyrimidine (Method 4, 150 mg, 0.42 mmol) and 3-(4-methyl-1-piperazinyl)propyl chloride dihydrochloride (120 mg, 0.48 mmol) in DMSO (2 ml) was heated at 100°C for 12 hours. Silica (1 g) was added and volatile material was removed by evaporation. The residue was loaded onto a Varian Mega Bond Elut column and the column was eluted with 50:50 iso-hexane : DCM (2 x 20 ml), DCM (2 x 20 ml), 2% 2M

NH_3/MeOH/DCM (2 x 20 ml), 4% 2M NH_3/MeOH/DCM (2 x 20 ml), 6% 2M NH_3/MeOH/DCM (2 x 20 ml) and 10% 2M NH_3/MeOH/DCM (8 x 20 ml). Concentration of the appropriate fractions gave the product as a yellow solid (35 mg, 17%). MS (MH^+): 497, 499; HPLC (RT): 2.74.

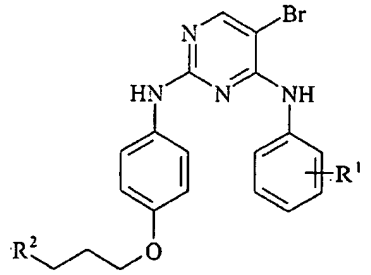
Example 184

4-Anilino-5-bromo-2-{3-[3-(4-methylpiperazin-1-yl)propoxy]anilino}pyrimidine

Using an analogous procedure to that described in Example 183, but starting from 4-anilino-5-bromo-2-(3-hydroxyanilino)pyrimidine (Method 6), the title product was obtained. MS (MH^+): 497, 499; HPLC (RT): 2.85.

Examples 185-192

The following compounds were prepared by an analogous method to that described in Example 136, starting from the appropriate substituted aniline (Methods 102-103, or obtained as described in Collect. Czech. Chem. Comm., 1990, 55, 282-95 and WO 9909030) and the appropriate 4-anilino-5-bromo-2-chloropyrimidine.



Ex	R^1	R^2	NMR	MS (MH^+)
185	H	Et_2N-	0.93 (t, 6H), 1.76 (tt, 2H), 2.43 (q, 4H), 2.50 (t, 2H), 3.91 (t, 2H), 6.72 (d, 2H), 7.10 (t, 1H), 7.32 (dd, 2H), 7.43 (d, 2H), 7.60 (d, 2H), 8.14 (s, 1H), 8.44 (s, 1H), 9.08 (s, 1H)	470.4, 472.4

186	H	Me_2N-	1.78 (tt, 2H), 2.11 (s, 6H), 2.32 (t, 2H), 3.91 (t, 2H), 6.72 (d, 2H), 7.11 (t, 1H), 7.32 (dd, 2H), 7.43 (d, 2H), 7.60 (d, 2H), 8.14 (s, 1H), 8.44 (s, 1H), 9.07 (s, 1H)	442.3, 444.3
187	3-Me	Me_2N-	HPLC (RT) 5.66	456, 458
188[1]	H	*i*-PrNH-	1.2 (d, 6H), 2.1 (m, 2H), 3 (m, 2H), 3.3 (m, 1H), 4.0 (t, 2H), 6.8 (d, 2H), 7.2 (t, 1H), 7.4 (m, 4H), 7.6 (d, 2H), 8.3 (s, 1H), 9.3 (br s, 1H), 9.5 (br s, 1H)	456, 458
189[1]	2-$HOCH_2$-	*i*-PrNH-	1.2 (d, 6H), 2.1 (m, 2H), 3.0 (m, 2H), 3.3 (m, 1H), 4.0 (t, 2H), 4.5 (s, 2H), 6.8 (d, 2H), 7.2 (m, 1H), 7.3 (m, 4H), 7.4 (d, 1H), 7.8 (d, 1H) 8.3 (s, 1H), 9.3 (br s, 1H), 9.5 (br s, 1H)	486, 488
190[1]	4-F	*i*-PrNH-	1.2 (d, 6H), 2.1 (m, 2H), 3.0 (m, 2H), 3.3 (m, 1H), 4.0 (t, 2H), 6.8 (d, 2H), 7.2 (m, 2H), 7.3 (m, 2H), 7.6 (d, 2H), 8.3 (s, 1H), 9.3 (br s, 1H), 9.5 (br s, 1H)	474, 476
191	H	imidazol-1-yl	2.2 (m, 2H), 3.9 (m, 2H), 4.4 (m, 2H), 6.7 (d, 2H), 7.2 (m, 1H), 7.4 (m, 4H), 7.5 (m, 2H), 7.7 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.2 (s, 1H), 9.3 (s, 1H), 9.5 (s, 1H)	465, 467
192	4-F	imidazol-1-yl	2.1 (m, 2H), 3.8 (m, 2H), 4.2 (m, 2H), 6.7 (d, 2H), 6.9 (s, 1H), 7.2 (m, 2H), 7.4 (m, 2H), 7.6 (m, 2H), 8.1 (s, 1H), 8.6 (s, 1H), 9.1 (s, 1H)	483, 485

[1] Isolated by filtration from the reaction mixture and washing with *n*-butanol and diethyl ether.

Example 193

4-Anilino-5-bromo-2-[4-(3-morpholinopropoxy)anilino]pyrimidine

Triphenylphosphine (400 mg, 1.5 mmol) was added to a stirred solution of 4-anilino-5-bromo-2-(4-hydroxyanilino)pyrimidine (Method 4, 178 mg, 0.5 mmol) in DCM (40 ml) and the solution was stirred for 30 minutes. A solution of 4-(3-hydroxypropyl)morpholine (80 mg, 1.5 mmol) in DCM (2 ml) was added and the solution was stirred for 2 minutes. Diethyl azodicarboxylate (0.25 ml, 1.5 mmol) was added dropwise and the mixture was stirred for 20 hours. Volatile material was removed by evaporation and the residue was dissolved into ethyl acetate (100 ml). The solution was washed with water (2 x 50 ml) and then extracted with 2M hydrochloric acid (2 x 30 ml). The combined acidic extracts were washed with ethyl acetate (2 x 50 ml) and then basified by addition of 0.88 ammonia solution. The basified solution was extracted with ethyl acetate (2 x 50 ml) and the extracts were washed with water (2 x 50 ml) and saturated sodium chloride (2 x 50 ml) and dried. Volatile material was removed by evaporation and the residue was loaded on a Varian Mega Bond Elut column. Elution with 0-10% methanol in ethyl acetate and evaporation of the appropriate fractions gave an oil, which was treated with methanolic hydrogen chloride. Volatile material was removed by evaporation and the residue was recrystallized from a mixture of methanol and ether to give the product as a dihydrochloride salt (28 mg). NMR: 2.2 (m, 2H), 3.1 (m, 2H), 3.2 (m, 2H), 3.4 (d, 2H), 3.8-4.1 (m, 6H), 6.8 (d, 2H), 7.2-7.3 (t, 1H), 7.3-7.5 (m, 4H), 7.6 (d, 2H), 8.4 (s, 1H), 9.5 (br s, 1H), 10.1 (br s, 1H), 11.3 (br s, 1H); MS (MH^+): 484, 486.

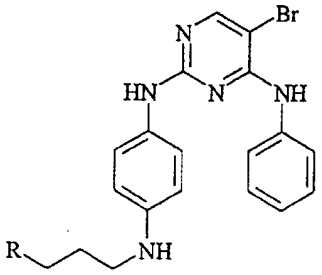
Example 194

5-Bromo-2-{4-[3-(*N,N*-dimethylamino)propoxy]anilino}-4-[(6-methylpyrid-2-yl)amino]pyrimidine

Using an analogous method to that described in Example 136, but starting from 5-bromo-2-chloro-4-[(6-methylpyrid-2-yl)amino]pyrimidine (Method 84) and 4-[3-(*N,N*-dimethylamino) propoxy]aniline (obtained as described in WO 9909030), the product was obtained. MS (MH^+): 457, 459; HPLC (RT): 5.26.

Examples 195-196

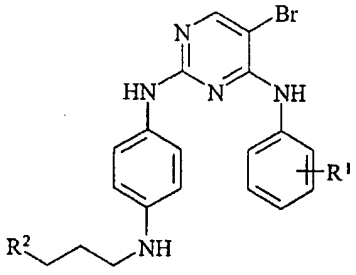
The following compounds were prepared by an analogous method to that described in Example 1, starting from 4-anilino-5-bromo-2-chloropyrimidine (Method 13) and the appropriate 4-substituted aniline (Methods 106-107).



Ex	R	NMR	MS (MH^+)
195	Me_2N-	2-2.1 (m, 2H), 2.7 (s, 6H), 3.1-3.2 (m, 2H), 3.3 (m, 2H), 7.1 (m, 2H), 7.2 (m, 1H) 7.4 (m, 2H), 7.5 (m, 2H), 7.6 (m, 2H), 8.3 (s, 1H), 9.3 (s, 1H)	441, 443
196	imidazol-1-yl	2.2 (m, 2H), 3.1-3.2 (m, 2H), 4.4 (m, 2H), 7.2 (m, 3H), 7.4 (m, 2H) 7.5 (m, 4H), 7.7 (s, 1H), 7.8 (s, 1H), 8.3 (s, 1H), 9.2 (s, 1H), 9.4 (s, 1H)	464, 466

Examples 197-215

The following compounds were prepared by an analogous method to that described in Example 1, starting from the appropriate 4-anilino-5-bromo-2-chloropyrimidine and the appropriate 4-substituted aniline (Methods 106-108).

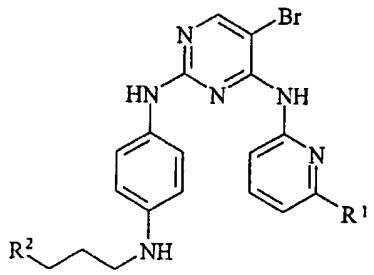


Ex	R^1	R^2	MS (MH^+)	HPLC (RT)
197	3-Me	Me_2N-	455, 457	4.13
198	3-Me	*i*-PrNH-	469, 471	4.51
199	4-F	imidazol-1-yl	482, 484	3.98
200	3-F	imidazol-1-yl	482, 484	4.65
201	4-MeS	imidazol-1-yl	510, 512	5.3
202	4-Br	imidazol-1-yl	543, 545	5.63
203	3,4-di-F	imidazol-1-yl	500, 502	4.94
204	4-F	Me_2N-	459, 461	4.37
205	3-F	Me_2N-	459, 461	4.26
206	4-Br	Me_2N-	519, 521, 523	5.16
207	3,4-di-F	Me_2N-	477, 479	4.60
208	3-F	*i*-PrNH-	473, 475	4.53
209	4-MeS	*i*-PrNH-	501, 503	5.26
210	3,4-di-F	*i*-PrNH-	491, 493	4.66
211	4-F	*i*-PrNH-	473, 475	4.25
212	4-Br	*i*-PrNH-	533, 535, 537	5.60
213	2-$HOCH_2$	imidazol-1-yl	494, 496	3.83
214	2-$HOCH_2$	*i*-PrNH-	485, 487	3.61[1]
215	2-$HOCH_2$	Me_2N-	471, 473	3.74

[1] Data obtained from a Hypersil 10 cm base deactivated reverse phase column, using 10-95% acetonitrile/water gradient, flow rate 1 ml/min over 10 minutes.

Examples 216-221

The following compounds were prepared by an analogous method to that described in Example 1, starting from the appropriate 5-bromo-2-chloro-4-(2-pyridylamino)pyrimidine and the appropriate 4-substituted aniline.

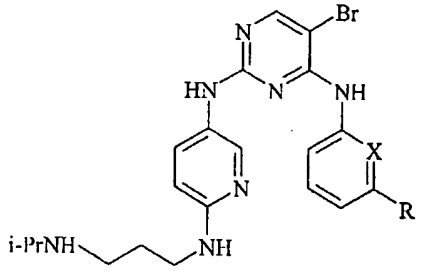


Ex	R^1	R^2	MS (MH^+)	HPLC (RT)
216	Me	Me_2N-	456, 458	3.21
217	Me	*i*-PrNH-	470, 472	3.22
218	Me	imidazol-1-yl	479, 481	4.07
219	H	imidazol-1-yl	465, 467	3.69
220	H	*i*-PrNH-	456, 458	1.80[1]
221	H	Me_2N-	442, 444	1.75

[1] Data obtained from a Hypersil 10 cm base deactivated reverse phase column, using 10-95% acetonitrile/water gradient, flow rate 2 ml/min over 10 minutes.

Examples 222-223

The following compounds were prepared by an analogous method to that described in Example 1, starting from the appropriate 4-substituted 5-bromo-2-chloropyrimidine and 5-amino-2-[3-(isopropylamino)propylamino]pyridine (Method 109).



Ex	X	R	MS (MH^+)	HPLC (RT)
222	CH	H	456, 458	3.06
223	N	Me	471, 473	4.06

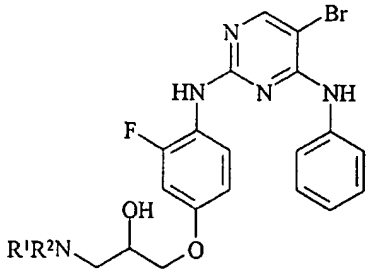
Example 224

4-Anilino-5-bromo-2-{4-[2-hydroxy-3-(*N',N'*-dimethylhydrazino)propoxy]anilino}pyrimidine

4-Anilino-5-bromo-2-[4-(2,3-epoxypropoxy)anilino]pyrimidine (Method 3, 100 mg, 0.24 mmol) was dissolved in THF (1 ml). *N,N*-Dimethylhydrazine (148 mg, 2.42 mmol) was added and the mixture was heated at 100°C for 1 hour. Volatile material was removed by evaporation and the residue was triturated with diethyl ether (2 ml) to give the product as a yellow solid (83 mg, 74%). MS (MH^+): 473, 475; HPLC (RT): 3.37.

Examples 225-230

The following compounds were prepared by an analogous method to that described in Example 224, starting from 4-anilino-5-bromo-2-[4-(2,3-epoxypropoxy)-2-fluoroanilino] pyrimidine (Method 2) and the appropriate amine.



Ex	R^1	R^2	MS (MH^+)	HPLC (RT)
225	*i*-Bu	H	504, 506	4.17
226	cyclopentyl	H	516, 518	4.56
227	pyrrolidino		503, 505	3.68
228	4-methylpiperazin-1-yl		531, 533	2.38
229	Me	Me	477, 479	3.11
230	Me_2N-	H	491, 493	3.23

Example 231

4-Anilino-5-bromo-2-{4-[3-ethoxy-2-(hydroxy)propoxy]anilino}pyrimidine

Using an analogous method to that described in Example 136, but starting from 4-anilino-5-bromo-2-chloropyrimidine (Method 13) and 4-[3-ethoxy-2-(hydroxy)propoxy] aniline (obtained as described in J. Med. Chem., 1998, 41, 330-36), the product was obtained in 21% yield. NMR: 1.10 (t, 3H), 3.42 (m, 2H), 3.45 (q, 2H), 3.75-3.9 (m, 3H), 4.99 (d, 1H), 6.74 (d, 2H), 7.12 (t, 1H), 7.33 (dd, 2H), 7.44 (d, 2H), 7.60 (d, 2H), 8.15 (s, 1H), 8.45 (s, 1H), 9.10 (s, 1H); MS (MH^+): 459.3, 461.4.

Example 232

4-Anilino-5-bromo-2-{4-[2,2-dimethyl-3-(*N,N*-dimethylamino)propylamino]anilino} pyrimidine

Using an analogous method to that described in Example 1, but starting from 4-anilino-5-bromo-2-chloropyrimidine (Method 13) and 4-[2,2-dimethyl-3-(*N,N*-dimethylamino)propylamino]aniline (Method 110), the product was obtained. NMR: 0.9 (s, 6H), 2.15 (s, 2H), 2.2 (s, 6H), 2.8 (d, 2H), 5.1 (m, 1H), 6.5 (d, 2H), 7.1 (m, 1H), 7.2 (m, 2H), 7.3 (m, 2H), 7.6 (m, 2H), 8.1 (s, 1H), 8.3 (s, 1H), 8.8 (s, 1H); MS (MH^+): 469, 471.

Example 233

4-Anilino-5-bromo-2-(4-{*N*-[2-hydroxy-3-(*N,N*-dimethylamino)propyl]-*N*-methylamino} anilino)pyrimidine

Using an analogous method to that described in Example 1, but starting from 4-anilino-5-bromo-2-chloropyrimidine (Method 13) and 4-{*N*-[2-hydroxy-3-(*N,N*-dimethylamino)propyl]-*N*-methylamino}aniline (Method 116), the product was obtained. MS (MH^+): 471, 473; HPLC (RT): 4.53.

Example 234

4-Anilino-5-bromo-2-{4-[2-hydroxy-2-methyl-3-(isopropylamino)propoxy]anilino} pyrimidine

Using an analogous method to that described in Example 1, but starting from 4-anilino-5-bromo-2-chloropyrimidine (Method 13) and 4-[2-hydroxy-2-methyl-3-(isopropyl-

amino)propoxy]aniline (Method 118), the product was obtained. MS (MH^+): 486, 488; HPLC (RT): 4.26.

Preparation of Starting Materials:

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the above reactions.

Method 1

4-Anilino-5-ethoxycarbonyl-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino} pyrimidine

Using an analogous method to that described in Example 1, but starting from 4-anilino-2-chloro-5-ethoxycarbonylpyrimidine (Method 11) and treating the material obtained after chromatography with ethereal hydrogen chloride, the product was obtained in 57% yield as a dihydrochloride salt. MS (MH^+): 464.5, 466.5.

Method 2

4-Anilino-5-bromo-2-[4-(2,3-epoxypropoxy)-2-fluoroanilino]pyrimidine

Potassium carbonate (1.1 g, 8.01 mmol) and epibromohydrin (402 mg, 2.94 mmol) were added to a solution of 4-anilino-5-bromo-2-(2-fluoro-4-hydroxyanilino)pyrimidine (Method 5; 1.0 g, 2.67 mmol) in DMF (3 ml), and the suspension was stirred at room temperature for 16 hours. Volatile material was removed by evaporation and the residue was stirred vigorously in water. The solid remaining was collected by filtration and dried under vacuum to give the product (1.1 g, 98%). MS (MH^+): 431.

Method 3

4-Anilino-5-bromo-2-[4-(2,3-epoxypropoxy)anilino]pyrimidine

Using an analogous procedure to that described in Method 2, but starting from 4-anilino-5-bromo-2-(4-hydroxyanilino)pyrimidine (Method 4), the product was obtained in 49% yield. MS (MH^+): 413.

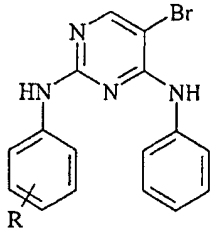
Method 4

4-Anilino-5-bromo-2-(4-hydroxyanilino)pyrimidine

4-Aminophenol (0.73 g, 7.8 mmol) and concentrated hydrochloric acid (1.30 ml, 7.1 mmol) were added to 4-anilino-5-bromo-2-chloropyrimidine (Method 13; 3.0 g, 7.1 mmol) in *n*-butanol (30 ml), and the mixture was heated at 100°C for 12 hours. The solid which precipitated out on cooling was filtered off and washed with *n*-butanol and diethyl ether to give the product (0.80 g, 32%). MS (MH^+): 357, 359.

Methods 5-6

The following intermediates were prepared by an analogous method to that described in Method 4, using the appropriate aminophenol.



Method	R	MS (MH^+)
5	2-F, 4-OH	375, 377
6	3-OH	357, 359

Method 7

4-Anilino-2,5-dichloropyrimidine

A solution of 2,4,5-trichloropyrimidine (Method 8; 5.5 g, 30.0 mmol), aniline (2.79 g, 30.0 mmol) and *N,N*-diisopropylethylamine (3.87 g, 30.0 mmol) in *n*-butanol (75 ml) was heated under reflux for 4 hours. Volatile material was removed by evaporation and the residue was dissolved in DCM (100 ml). The solution was washed with water (3 x 100 ml) and saturated brine (100 ml) and dried. Volatile material was removed by evaporation and the residue was purified by column chromatography on silica gel, eluting with 15% ethyl acetate/isohexane, to give the product as an oil which solidified on standing (3.94 g, 54%).

NMR: 7.2 (t, 1H), 7.4 (t, 2H), 7.6 (d, 2H), 8.4 (s, 1H), 9.45 (br s, 1H); MS (MH^+): 240, 242, 244.

Method 8

2,4,5-Trichloropyrimidine

5-Chlorouracil (10.0 g, 68.5 mmol) was dissolved in phosphorus oxychloride (60 ml) and phosphorus pentachloride (16.0 g, 77.0 mmol) was added. The mixture was heated under reflux for 16 hours, left to cool and then poured slowly into water (200 ml) with vigorous stirring. The mixture was stirred for 1.5 hours and then ethyl acetate (250 ml) was added. The organic layer was separated and the aqueous layer was extracted with a further portion of ethyl acetate (250 ml). The combined extracts were washed with saturated sodium bicarbonate (200 ml) and saturated sodium chloride (200 ml), and then dried. Volatile material was removed by evaporation and the residue was purified by column chromatography, eluting with DCM, to give the product as a yellow liquid (6.37 g, 51%). NMR ($CDCl_3$): 8.62 (s, 1H); MS (MH^+): 182, 184, 186.

Method 9

4-Anilino-2-chloro-5-(*N*-isopropylcarbamoyl)pyrimidine

A solution of aniline (0.292 ml, 3.2 mmol) and triethylamine (0.447 ml, 3.21 mmol) in THF (5 ml) was added dropwise over 10 minutes to a solution of 2,4-dichloro-5-(*N*-isopropyl-carbamoyl)pyrimidine (Method 10, 0.75 g, 3.2 mmol) in distilled THF (8 ml) at -10°C under nitrogen. The solution was stirred at -10°C for 1 hour and at room temperature for 2 days. Insoluble material was removed by filtration and the filtrate was diluted with ethyl acetate (20 ml). The solution was washed with water (20 ml) and saturated sodium chloride (20 ml), and then dried. Volatile material was removed by evaporation and the residue was recrystallized from DCM to give the product as a white solid (0.34 g), which was used without characterisation.

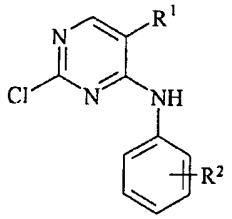
Method 10

2,4-Dichloro-5-(*N*-isopropylcarbamoyl)pyrimidine

A solution of isopropylamine (1.28 ml, 15.0 mmol) and triethylamine (2.10 ml, 15.1 mmol) in dry THF (5 ml) was added dropwise over 30 minutes to a solution of 2,4-dichloropyrimidine-5-carbonyl chloride (obtained as described in J. Med. Chem., 1972, 15, 200; 3.18 g, 15.0 mmol) in dry THF (8 ml) at -10°C. The solution was stirred 0°C for 2 hours, filtered and evaporated to dryness to yield the product (0.93 g), which was used without further purification.

Methods 11-59

The following intermediates were prepared by an analogous method to that described in Method 7, using the appropriate substituted aniline and 5-substituted 2,4-dichloropyrimidine (Methods 7, 60-61, or obtained as described in J. Org. Chem., 1955, 20, 837; J. Chem. Soc., 1960, 4590; Annalen, 1966, 692, 119; WO9204901; Eur. J. Med. Chem., 1991, 26, 557; Tet. Lett., 1993, 34, 1605).



Method	R^1	R^2	MS (MH^+)
11	$EtCO_2$-	H	278.2, 280.2
12	Me	H	220.2, 222.2
13	Br	H	284, 286, 288
14	Br	2-Ph	360.1, 362.1, 364.1
15	Br	3,4-$(CH_2)_3$ **	324.1, 326.1, 328.1
16	Br	2-F, 5-Me	316.1, 318.1, 320.1
17	NO_2	2-F	269, 271
18	Br	2-Br, 4-Me	376.0, 378.0, 380.0, 382.0
19	Br	2-morpholino	367.1, 369.1, 371.2 (MH^+)

20	Br	4-Br	360.0, 362.0, 364.0, 366.0 (MH^-)
21	Me	3-Cl	254, 256, 258
22	Cl	2-Cl, 5-Me	288.0, 290.1, 292.1
23	Cl	2-morpholino	325.1, 327.2, 329.2
24	Cl	4-Br	316.0, 318.0, 320.0, 322.0, (MH^-)
25	Br	2-$PhCH_2$-	374, 376
26	Br	2-OPh	376, 378
27	Br	2-$PhCH_2O$-	390, 392
28	F	H	224.1, 226.1
29	F	2-Cl, 5-Me	272.2, 274.2, 276.2
30	F	2-morpholino	309.2, 311.2
31	F	4-Br	302.0, 304.0, 306.2
32	morpholino	H	291, 293
33	Br	4-$PhCH_2O$-	390, 392
34	Br	3-PhO-	376, 378
35	Br	4-PhO-	376, 378
36	Br	3-$PhCH_2O$-	390, 392
37	Br	4-$PhCH_2$-	374, 376
38	Cl	3,4-di-Cl	306.1, 308.0, 310.0, 312.1, (MH-)
39	Cl	2-F, 5-Me	272.1, 274.2, 276.2
40	Cl	3,4-$(CH_2)_3$ **	280.2, 282.2, 284.2
41	Cl	2-CN	265.1, 267.1, 269.1
42	EtO-	H	250, 252
43	Br	4-$HOCH_2$-	314, 316, 318
44	CH_2=CH-	H	232, 234
45	MeO-	H	236, 238
46	Br	3-CF_3	352, 354
47	Br	4-CF_3	352, 354
48	$EtOCH_2$-	H	
49	Br	2,4-di-F	318, 320

50	Br	4-MeO	314, 316
51	Br	2-$HOCH_2$-	314, 316
52[2]	Br	4-F	
53[3]	Br	3,4-di-F	
54	Br	3-Me	298, 300, 302
55	Cl	4-F	258, 260
56[4]	Br	3-F	
57[5]	Br	4-MeS-	
58	PhCH(OH)-	H	312.2, 314.2
59	I	H	331, 333

[1] NMR: 1.31 (t, 3H), 3.58 (q, 2H), 4.55 (s, 2H), 7.12 (t, 1H), 7.37 (dd, 2H), 7.60 (d, 2H), 7.97 (s, 1H), 8.29 (br s, 1H).

[2] NMR: 7.22 (m, 2H), 7.55 (m, 2H), 8.42 (s, 1H), 9.32 (s, 1H).

[3] NMR: 7.42 (m, 2H), 7.72 (m, 1H), 8.47 (s, 1H), 9.37 (s, 1H).

[4] NMR: 6.97 (m, 1H), 7.45 (m, 3H), 8.48 (s, 1H), 9.35 (s, 1H).

[5] NMR: 2.50 (s, 3H), 7.27 (d, 2H), 7.47 (d, 2H) 8.42 (s, 1H), 9.23 (s, 1H).

** Such that R^2 and the phenyl ring to which it is attached forms indan-5-yl.

Method 60

2,4-Dichloro-5-(4-morpholino)pyrimidine

5-(4-Morpholino)uracil (obtained as described in J. Amer. Chem. Soc., 1951, 73, 1061; 750 mg, 3.8 mmol) and *N,N*-dimethylaniline (0.6 ml, 4.7 mmol) were added to phosphorous oxychloride (20 ml). The mixture was heated under reflux for 4 hours and then concentrated by evaporation. Water (40 ml) was added and the mixture was extracted with ethyl acetate (2 x 30 ml). The extracts were washed with 2M hydrochloric acid (20 ml) and water (20 ml) and then dried. Volatile material was removed by evaporation and the residue was purified by column chromatography, eluting with 33% ethyl acetate in isohexane, to give the product as a white solid (380 mg, 40 %). NMR: 3.1 (t, 4H), 3.7 (t, 4H), 8.5 (s, 1H).

Method 61

2,4-Dichloro-5-ethoxypyrimidine

Using an analogous method to that described in Method 8, but starting from 5-ethoxyuracil (obtained by an analogous method to that described for the preparation of 5-methoxyuracil in J. Chem. Soc., 1960, 4590), the product was obtained in 25% yield. NMR ($CDCl_3$): 1.45 (t, 3H), 4.15 (q, 2H), 8.1 (s, 1H).

Method 62

2-Chloro-4-(3,4-dichloroanilino)-5-methylpyrimidine

3,4-Dichloroaniline (639 mg, 3.94 mmol) and concentrated hydrochloric acid (ca. 12M, 0.2 ml, ca. 2.4 mmol) were sequentially added to a solution of 5-methyl-2,4-dichloropyrimidine (643 mg, 3.94 mmol) in *n*-butanol (20 ml). The mixture was stirred at ambient temperature for 20 hours, after which time a gelatinous precipitate had fallen out of solution. DCM was added until a solution was obtained, and silica (2.5 g) was added. Volatile material was removed by evaporation and the residue was loaded on a Varian Mega Bond Elut column pre-conditioned with ethyl acetate. The column was eluted with 0-10% methanol solution in ethyl acetate containing 0.5% aqueous ammonia. The appropriate fractions were concentrated, and the residue was triturated with *n*-butanol (20 ml). The filtrate was evaporated onto silica (2.5 g) and loaded on a Varian Mega Bond Elut column pre-conditioned with isohexane. The column was eluted with 0-50% ethyl acetate solution in isohexane. Concentration of the appropriate fractions gave the product as a white solid (340 mg, 26%). NMR: 2.17 (s, 3H), 7.60 (d, 1H), 7.70 (dd, 1H), 8.00 (d, 1H), 8.11 (s, 1H), 8.97 (s, 1H); MS (MH^+): 288.1, 290.1, 292.1.

Method 63

4-Anilino-5-benzyl-2-chloropyrimidine

Triethylsilane (0.14 ml, 1.10 mmol) was added to a solution of 4-anilino-2-chloro-5-[1-hydroxy-1-phenylmethyl]pyrimidine (Method 58; 170 mg, 0.55 mmol) in trifluoroacetic acid (1.5 ml), and the mixture was stirred for 64 hours. Water (20 ml) was added and the mixture was neutralised with sodium carbonate powder and extracted with DCM (3 x 20 ml). The extracts were combined, washed with water (30 ml), dried, concentrated to a volume of 5

ml, and loaded on a Varian Mega Bond Elut column. Elution with DCM and concentration of the appropriate fractions gave the product as a yellow crystalline solid (42 mg, 26%). NMR ($CDCl_3$): 3.93 (s, 2H), 6.45 (br s, 1H), 7.08 (m, 1H), 7.2-7.4 (m, 9H), 8.09 (s, 1H); MS (MH^+): 296.2, 298.2.

Method 64

4-Anilino-5-cyano-2-(methanesulphonyl)pyrimidine

3-Chloroperoxybenzoic acid (57-86%; 2.67 g, 8.8-13.3 mmol) was added in aliquots to a solution of 4-anilino-5-cyano-2-(methylthio)pyrimidine (Method 65; 1.0 g, 4.13 mmol) in chloroform (100 ml), and the mixture was stirred for 2 hours. The mixture was washed with saturated sodium bicarbonate (100 ml), water (100 ml), and saturated sodium chloride (100 ml) and dried. Volatile material was removed by evaporation and the residue was taken up in DCM (10 ml). The solution was loaded onto a silica column pre-equilibrated with 20% ethyl acetate solution in isohexane. Elution with 20-50% ethyl acetate in isohexane and concentration of the appropriate fractions gave the product as a yellow solid (680 mg, 61%). NMR ($CDCl_3$): 3.26 (s, 3H), 7.30 (t, 1H), 7.44 (dd, 2H), 7.57 (d, 2H), 7.65 (br s, 1H), 8.71 (s, 1H); MS (MH^+): 274.9.

Method 65

4-Anilino-5-cyano-2-(methylthio)pyrimidine

Using a method analogous to that described in Method 7, but starting from 4-chloro-5-cyano-2-(methylthio)pyrimidine (obtained as described in J. Het. Chem. 1971, 8, 445) and performing the reaction at 85°C, the product was obtained in 93% yield. NMR ($CDCl_3$): 2.51 (s, 3H), 7.15 (br s, 1H), 7.20 (t, 1H), 7.40 (dd, 2H), 7.57 (d, 2H), 8.38 (s, 1H).

Method 66

4-Anilino-2-chloro-5-(4-phenyl-1-butynyl)pyrimidine

A solution of 4-anilino-2-chloro-5-iodopyrimidine (Method 59; 662 mg, 2.0 mmol), 4-phenyl-1-butyne (260 mg, 2.0 mmol) and triethylamine (0.56 ml, 4.0 mmol) in THF (20 ml) was purged with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (25 mg) and cuprous iodide (12.5 mg) were added and the mixture was stirred for 20 hours. Insoluble material was

removed by filtration and washed with diethyl ether (50 ml). The filtrate and washings were combined and concentrated, and the residue was purified by bond elute chromatography, eluting with 25% ethyl acetate in isohexane, to give the product (0.5 g). NMR ($CDCl_3$): 2.85 (m, 2H), 2.95 (m, 2H), 7.05 (m, 2H), 7.1-7.4 (m, 7H), 7.45 (dd, 2H), 8.2 (s, 1H); MS (MH^+): 334, 336.

Method 67

4-Anilino-2-chloro-5-(3-cyclopentyl-1-propynyl)pyrimidine

Using an analogous method to that described Method 66, but starting from 3-cyclopentylpropyne, the product was obtained in 72% yield. NMR ($CDCl_3$): 1.3-1.4 (m, 2H), 1.6-1.8 (m, 4H), 1.8-2.0 (m, 2H), 2.2 (m, 1H), 2.55 (d, 2H), 7.15 (t, 1H), 7.5-7.5 (m, 3H), 7.65 (d, 2H), 8.2 (s, 1H); MS (MH^+): 312, 314.

Method 68

trans-4-Anilino-2-chloro-5-(2-phenylethenyl)pyrimidine

A solution of 4-anilino-2-chloro-5-iodopyrimidine (Method 59, 331 mg, 1 mmol), styrene (130 mg, 1.2 mmol), triethylamine (0.5 ml) and palladium acetate (20 mg) in acetonitrile (10 ml) was heated at 80°C for 20 hours. The solution was poured into water (100 ml) and the mixture was extracted with ethyl acetate (2 x 50 ml). The extracts were washed with water (2 x 50 ml) and saturated sodium chloride (50 ml) and dried. Volatile material was removed by evaporation and the residue was purified by bond elute chromatography, eluting with 10% ethyl acetate in isohexane, to give the product (40 mg). NMR ($CDCl_3$): 6.8 (d, 1H), 7.0 (d, 2H), 7.15 (t, 1H), 7.3-7.45 (m, 5H), 7.5 (d, 2H), 7.6 (d, 2H), 8.2 (s, 1H); MS (MH^+): 308, 310.

Method 69

trans-4-Anilino-2-chloro-5-[2-(4-fluorophenyl)ethenyl]pyrimidine

Using an analogous method to that described Method 68, but starting from 4-fluorostyrene, the product was obtained in 10% yield.

Method 70

4-Anilino-2-chloro-5-phenylpyrimidine

Phenylboronic acid (240 mg, 2 mmol) and tetrakis(triphenylphosphine)palladium(0) (30 mg) were added to a solution of 4-anilino-2-chloro-5-iodopyrimidine (Method 59, 331 mg, 1 mmol) in toluene (10 ml) and ethanol (2.5 ml). 2M aqueous sodium carbonate solution (10 ml) was added and the mixture was stirred and heated under reflux for 3 hours. Further portions of phenylboronic acid (240 mg, 2 mmol) and tetrakis(triphenylphosphine) palladium(0) (30 mg) were added and the mixture was stirred and heated under reflux for 20 hours. The mixture was poured into water (100 ml) and extracted with ethyl acetate (2 x 50 ml). The combined extracts were washed with water (2 x 50 ml) and saturated sodium chloride (50 ml) and dried. Volatile material was removed by evaporation and the residue was purified by bond elute chromatography, eluting with 10-25% ethyl acetate in isohexane, to give the product (140 mg). NMR ($CDCl_3$): 6.85 (s, 1H), 7.1 (t, 1H), 7.3 (t, 2H), 7.4 (m, 2H), 7.5-7.6 (m, 6H), 8.05 (s, 1H); MS (MH^+): 282, 284.

Method 71

4-Anilino-2-chloro-5-(2-phenylethyl)pyrimidine

4-Anilino-2-chloro-5-(2-phenylethynyl)pyrimidine (Method 72; 400 mg) was dissolved in ethyl acetate (100 ml) and the solution was purged with nitrogen. 5% Rhodium on carbon (50 mg) was added and the mixture was hydrogenated at standard temperature and pressure (STP) for 20 hours. A further portion of 5% rhodium on carbon catalyst (50 mg) was added and the solution was hydrogenated at STP for a further 3 hours. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by bond elute chromatography, eluting with 0-10% ethyl acetate in isohexane, to give the product (70 mg). NMR ($CDCl_3$): 2.8 (t, 2H), 3.0 (t, 2H), 6.25 (s, 1H), 7.1 (m, 1H), 7.15-7.4 (m, 9H), 7.95 (s, 1H); MS (MH^+): 310, 312.

Method 72

4-Anilino-2-chloro-5-(2-phenylethynyl)pyrimidine

Using an analogous method to that described Method 67, but starting from phenyl acetylene, the product was obtained in 57% yield. NMR ($CDCl_3$): 7.2 (t, 1H), 7.4-7.5 (m, 5H), 7.5 (br s, 1H), 7.5-7.6 (m, 2H), 7.7 (d, 2H), 8.4 (s, 1H); MS (MH^+): 306, 308.

Method 73

4-Anilino-2-chloro-5-fur-3-ylpyrimidine

A solution of 4-anilino-2-chloro-5-iodopyrimidine (Method 59, 331 mg, 1 mmol), 3-furylboronic acid (224 mg, 2 mmol), caesium fluoride (400 mg, 2mmol) and tetrakis(triphenylphosphine)palladium(0) (30 mg) in THF (10 ml) was stirred and heated at reflux for 20 hours under a nitrogen atmosphere. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was purified by bond elute chromatography, eluting with 25% ethyl acetate in isohexane, to give the product (140 mg). NMR ($CDCl_3$): 6.6 (d, 1H), 7.0 (br s, 1H), 7.15 (t, 1H), 7.25 (s, 1H), 7.4 (t, 2H), 7.55 (d, 2H), 7.65 (d, 2H), 8.1 (s, 1H); MS (MH^+): 272, 274.

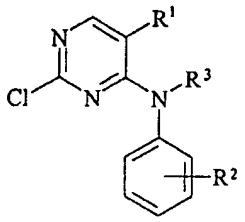
Method 74

4-[4-Bromo-*N*-(4,4,4-trifluorobutyl)anilino]-2,5-dichloropyrimidine

A mixture of 4-(4-bromoanilino)-2,5-dichloropyrimidine (Method 24; 315 mg, 1.0 mmol), 4,4,4-trifluoro-1-bromobutane (228 mg, 1.20 mmol) and potassium carbonate (165 mg, 1.20 mmol) in DMF (3 ml) was stirred at room temperature for 12 hours. Silica (2.5 g) was added and volatile material was removed by evaporation. The residue was purified by column chromatography, eluting with 0-40% ethyl acetate in isohexane, to give the product (187 mg). NMR: (373K); 1.84 (m, 2H), 2.28 (m, 2H), 3.99 (t, 2H), 7.22 (d, 2H), 7.58 (d, 2H), 8.23 (s, 1H); MS (MH^+): 428.2, 430.2, 432.2.

Methods 75-78

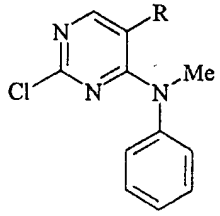
The following intermediates were prepared by an analogous method to that described in Method 74, using the appropriate 4-anilino-2-chloro-5-halopyrimidine (Methods 7, 13, 15, 24) and the appropriate alkyl halide.



Method	R^1	R^2	R^3	MS (MH^+)
75	Br	H	$-(CH_2)_3CF_3$	394.1, 396.1, 398.1
76	Cl	H	$-(CH_2)_3CF_3$	350.2, 352.2
77	Cl	4-Br	$-CH_2CH=CHBr$	436.1, 438.1, 440.1, 442.1
78	Cl	2-F, 5-Me	$-CH_2CH=CHPh$	388.3, 390.3

Methods 79-80

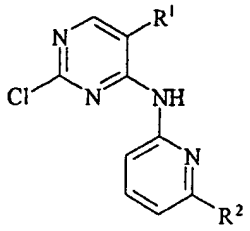
The following intermediates were prepared by an analogous method to that described in Method 7, using the appropriate 2,4-dichloro-5-halopyrimidine and *N*-methylaniline:



Method	R	MS (MH^+)
79	Cl	252, 254
80	Br	298, 300

Methods 81-84

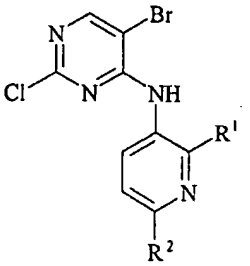
The following intermediates were prepared by an analogous method to that described in Method 7, using the appropriate 2-aminopyridine and 2,4-dichloro-5-halopyrimidine.



Method	R^1	R^2	MS (MH^+)
81	Br	H	285, 287
82	Cl	Me	254, 256
83	Cl	H	240, 242
84	Br	Me	299, 301

Methods 85-86

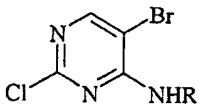
The following intermediates were prepared by an analogous method to that described in Method 7, using the appropriate 3-aminopyridine and 5-bromo-2,4-dichloropyrimidine.



Method	R^1	R^2	MS (MH^+)
85	NH_2	H	300, 302
86	H	MeO-	

Methods 87-88

The following intermediates were prepared by an analogous method to that described in Method 7, using the appropriate amino heterocycle and 5-bromo-2,4-dichloropyrimidine.



Method	R	MS
87	4-methylthiazol-2-yl	303, 305 (MH^+)
88	5-methylpyrazol-3-yl	288, 290 (MH^+)

Method 89

4-[2-Hydroxy-3-(*N,N*-dimethylamino)propoxy]aniline hydrochloride

A solution of 4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]nitrobenzene (Method 90, 3.75 g) in ethanol (40 ml) was catalytically hydrogenated over 10% palladium-on-carbon (0.4 g) overnight. The catalyst was removed by filtration through diatomaceous earth and the filtrate was concentrated. The residue was dissolved in diethyl ether containing a small amount of isopropanol and ethereal hydrogen chloride (1M, 16 ml) was added. Diethyl ether was removed by evaporation and the solid residue was suspended in isopropanol. The mixture was heated on a steam bath for several minutes and then allowed to cool. The insoluble solid was collected by filtration, washed with isopropanol and ether, and dried to give the product (3.04 g, 72.4%). NMR: 2.80 (s, 6H), 3.15 (m, 2H), 3.88 (m, 2H), 4.25 (m, 1H), 5.93 (br s, 1H), 6.88 (m, 4H); MS (MH^+): 211; $C_{11}H_{18}N_2O_2$.1.6 HCl requires: C; 49.2, H; 7.4, N; 10.4, Cl; 21.7%; found: C; 49.2, H; 7.2, N; 10.1; Cl; 19.1%.

Method 90

4-[2-Hydroxy-3-(*N,N*-dimethylamino)propoxy]nitrobenzene

4-(2,3-Epoxypropoxy)nitrobenzene (obtained as described in Synthetic Communications, 1994, 24, 833; 4.3 g,) was dissolved in methanol (30 ml) and DMF (10 ml). A solution of dimethylamine in methanol (2M, 17 ml) was added and the mixture was stirred overnight. Volatile material was removed by evaporation and the residue was partitioned between saturated sodium bicarbonate (100 ml) and ethyl acetate (100 ml). The organic layer was separated and washed with saturated sodium chloride (2 x 100 ml) and dried. Concentration gave the product as an oil that slowly crystallised under high vacuum (4.79 g,

89.9%). NMR ($CDCl_3$): 2.33 (s, 6H), 2.98 (m, 1H), 2.54 (m, 1H), 4.00 (m, 3 H), 7.00 (d, 2H), 8.20 (d, 2H); MS (MH^+): 241.

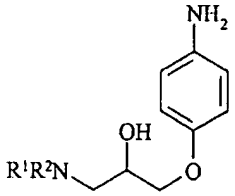
Method 91

4-{2-Hydroxy-3-[(4-methyl-1-piperazino)propoxy]}aniline

N-Methylpiperazine (8.50 ml, 51.2 mmol) was added to a solution of 4-(2,3-epoxypropoxy)nitrobenzene (obtained as described in Synthetic Communications, 1.00 g, 5.12 mmol) in THF (1 ml). The solution was heated under reflux for 3 hours and then concentrated on a rotary evaporator under high vacuum at 50°C for 1 hour. The residue was dissolved in methanol (5 ml) and 10% palladium on carbon (0.50 g) and ammonium formate (3.23 g, 51.2 mmol) were added. The reaction mixture was heated under reflux for 3 hours and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure to give the product as dark brown oil (1.35 g, 100%), which was used without further purification. MS (MH^+): 266.5.

Methods 92-101

The following intermediates were prepared by an analogous method to that described in Method 91, using the appropriate amine.



Method	R^1	R^2	MS (MH^+)
92[1]	$PhCH_2$-	i-Pr	315.4
93[1]	CH_2=$CHCH_2$-	Me	236.9
94	*i*-Bu	H	238.9
95	cyclopentyl	H	250.9
96	pyrrolidino		236.9
97[2]	Me	H	196.9
98[2]	H	H	182.9

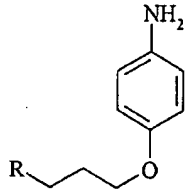
99[2]	Et	H	210.9
100	morpholino		252.9
101	4-acetylpiperazin-1-yl		296.9

[1] The intermediate substituted nitrobenzene was reduced by a different method. The residue was dissolved in ethanol (2.5 ml) and water (2.5 ml) and warmed to 80°C. Sodium dithionite (2.67 g, 15.4 mmol) was added over a period of 20 minutes. Insoluble material was removed by filtration and the filtrate was concentrated. The reside was suspended in 10% aqueous sodium bicarbonate (10 ml) and the mixture was extracted with DCM (20 ml). The extracts were washed with water (10 ml) and concentrated under reduced pressure to afford the product as an orange oil, which was used without further purification.

[2] Prepared from the corresponding *N*-benzyl substituted precursors. For complete de-benzylation, the reactions required a further addition of palladium on carbon (0.50 g) and ammonium formate (3.23 g mmol).

Methods 102-103

The following intermediates were prepared by an analogous method to that described in Method 89, using the appropriate nitrobenzene (Methods 104-105).



Method	R	MS (MH^+)
102	*i*-PrNH	209
103	imidazol-1-yl	218

Method 104

4-(3-Isopropylaminopropoxy)nitrobenzene

Potassium carbonate (1.0 g, 5.0 mmol) was added to a solution of 4-(3-bromopropoxy) nitrobenzene (obtained as described in Synthesis, 1990, 1069; 1.0 g, 3.9 mmol) in DMF (30 ml). Isopropylamine (0.4 ml, 4.6 mmol) was added and the mixture was heated at 60°C for 2

hours. Volatile material was removed by evaporation and the residue was dissolved in ethyl acetate (200 ml). The solution was washed with water (3 x 25ml) and saturated sodium chloride (25 ml) and then dried. The solvent was removed by evaporation and the residue was dissolved in isopropanol (10 ml). Ethereal hydrogen chloride (2M; 2 ml) was added and the precipitated solid was collected to give the product as a hydrochloride salt (0.60 g, 65%). MS (MH^+): 239.

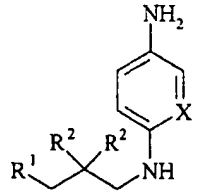
Method 105

4-[3-(Imidazol-1-yl)propoxy]nitrobenzene

A mixture of imidazole (0.8 g, 11.6 mmol) and 4-(3-bromopropoxy)nitrobenzene (1.5 g, 5.8 mmol) in 1,4-dioxane (75 ml) was heated at 100°C for 12 hours. Volatile material was removed by evaporation and the residue was dissolved in ethyl acetate (150 ml). The solution was washed with saturated sodium bicarbonate (3 x 50 ml), water (3 x 50 ml) and saturated sodium chloride (50 ml) and then dried. The solvent was removed by evaporation and the residue was purified by column chromatography, eluting with 0-5% methanol in DCM, to give the product as a yellow oil (0.51 g, 22%). MS (MH^+): 248.

Methods 106-110

The following intermediates were prepared by an analogous method to that described in Method 89, using the appropriate nitrobenzene (Methods 111-115).



Method	X	R^1	R^2	MS (MH^+)
106	CH	Me_2N	H	194
107	CH	imidazol-1-yl	H	217
108	CH	*i*-PrNH	H	208
109	N	*i*-PrNH	H	209
110	CH	Me_2N	Me	222

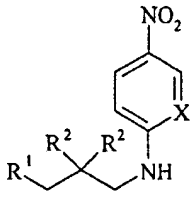
Method 111

4-[3-(*N,N*-dimethylamino)propylamino]nitrobenzene

N,N-Dimethylpropane-1,3-diamine (4.90 ml, 39 mmol) and potassium carbonate (6.37 g, 46 mmol) were added to 1-fluoro-4-nitrobenzene (5.0 g, 35 mmol) and the mixture was heated at 70°C for 3 hours. Insoluble material was removed by filtration and the filtrate was concentrated. The residue was dissolved in ethyl acetate (100 ml) and the solution was washed with water (3 x 100ml) and saturated sodium chloride (100 ml) and dried. The solvent was removed by evaporation to give the product as a yellow oil (8.57 g). MS (MH^+): 248.

Methods 112-115

The following intermediates were prepared by an analogous method to that described in Method 111, using the appropriate amine and 1-fluoro-4-nitrobenzene or 2-chloro-5-nitropyridine.



Method	X	R^1	R^2	MS (MH^+)
112	CH	imidazol-1-yl	H	246
113	CH	i-PrNH	H	238
114	N	i-PrNH	H	239
115	CH	Me_2N	Me	252

Method 116

4-{*N*-[2-Hydroxy-3-(*N,N*-dimethylamino)propyl]-*N*-methylamino}aniline

Using an analogous method to that described in Method 89, but starting from 4-{*N*-[2-hydroxy-3-(*N,N*-dimethylamino)propyl]-*N*-methylamino}nitrobenzene (Method 117), the product was obtained. MS (MH^+): 224.

Method 117

4-{*N*-[2-Hydroxy-3-(*N*,*N*-dimethylamino)propyl]-*N*-methylamino}nitrobenzene

Sodium hydride (60% dispersion in oil; 290 mg, 7.2 mmol) was added portionwise over 30 minutes to a solution of 4-nitro-*N*-methylaniline (1.0 g, 6.6 mmol) in DMF (30 ml) at 0°C. Epibromohydrin (0.62 ml, 7.2 mmol) was added dropwise to the solution at 0°C and the mixture was left to stand overnight. Volatile material was removed by evaporation and the residue was dissolved in a solution of dimethylamine in methanol (5.6M, 132 mmol). The solution was left to stand for 12 hours and then concentrated. The residue was dissolved in DCM (200 ml) and the solution was washed with water (3 x 20ml) and saturated sodium chloride (20 ml) and dried. Evaporation gave the product as an orange solid (1.44 g, 86%). MS (MH^+): 254.

Method 118

4-[2-Hydroxy-2-methyl-3-(isopropylamino)propoxy]aniline

Using an analogous method to that described in Method 89, but starting from 4-[2-hydroxy-2-methyl-3-(isopropylamino)propoxy]nitrobenzene (Method 119), the product was obtained in 52% yield. MS (MH^+): 239.

Method 119

4-[2-Hydroxy-2-methyl-3-(isopropylamino)propoxy]nitrobenzene

A mixture of 4-nitrophenol (1.0 g, 7.1 mmol), potassium carbonate (1.30 g, 9.4 mmol) and 2-chloromethyl-2-methyloxirane (0.84 g, 7.9 mmol) in DMF (50 ml) was stirred for 12 hours and then heated at 80°C for 12 hours. Insoluble material was removed by filtration and washed with DMF (10 ml). The combined filtrate and washings were concentrated and the residue was dissolved in methanol (20 ml). Isopropylamine (6.13 ml, 71 mmol) was added and the mixture was stirred for 12 hours. Volatile material was removed by evaporation and the residue was purified by bond elute chromatography, eluting with 0-5% methanol in DCM, to give the product as a yellow solid (0.5 g, 26%). MS (MH^-): 269.

Example 235

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)
Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	10 mg/ml
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

(g): Injection III	(1mg/ml, buffered to pH6)
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

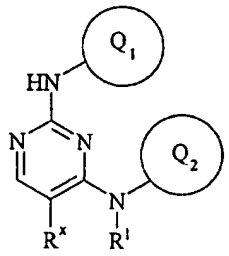
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

Claims

CLAIMS

What we claim is:

1. A pyrimidine derivative of the formula **(I)**:



(I)

wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl [optionally substituted by one or two substituents independently selected from halo, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, hydroxy, cyano, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, carbamoyl, -NHCOC_{1-4}alkyl, trifluoromethyl, phenylthio, phenoxy, pyridyl, morpholino], benzyl, 2-phenylethyl, C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent, or one phenyl substituent], *N*-phthalimido-C_{1-4}alkyl, C_{3-5}alkynyl [optionally substituted by one phenyl substituent] and C_{3-6}cycloalkyl-C_{1-6}alkyl;

wherein any phenyl or benzyl group in R^1 is optionally substituted by up to three substituents independently selected from halo, hydroxy, nitro, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, cyano, trifluoromethyl, C_{1-3}alkyl [optionally substituted by 1 or 2 substituents independently selected from halo, cyano, amino, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, hydroxy and trifluoromethyl], C_{3-5}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{3-5}alkynyl, C_{1-3}alkoxy, mercapto, C_{1-3}alkylthio, carboxy, C_{1-3}alkoxycarbonyl;

R^x is selected from halo, hydroxy, nitro, amino, cyano, mercapto, carboxy, sulphamoyl, formamido, ureido or carbamoyl or a group of formula **(Ib)**:

A-B-C-

(Ib)

wherein:

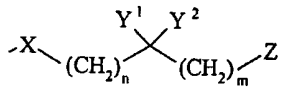
A is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl, wherein said C_{1-6}alkyl, C_{3-6}alkenyl and C_{3-6}alkynyl are optionally substituted by one or more substituents selected from halo, nitro, cyano, amino, hydroxy, mercapto, carboxy, formamido, ureido, C_{1-3}alkylamino, di-(C_{1-3}alkyl)amino, C_{1-3}alkoxy, trifluoromethyl, C_{3-8}cycloalkyl, phenyl, heterocycle or heteroaryl; wherein any phenyl, C_{3-8}cycloalkyl, heterocycle or heteroaryl may be optionally substituted by one or more halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, formamido, ureido, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, *N*-C_{1-4}alkylcarbamoyl, *N,N*-di-(C_{1-4}alkyl)carbamoyl, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl and C_{1-4}alkoxycarbonyl;

B is -O-, -S-, -C(O)-, -NH-, -N(C_{1-4}alkyl)-, -C(O)NH-, -C(O)N(C_{1-4}alkyl)-, -NHC(O)-, -N(C_{1-4}alkyl)C(O)- or B is a direct bond;

C is C_{1-4}alkylene or a direct bond;

Q_1 and Q_2 are independently selected from aryl, a 5- or 6-membered monocyclic moiety (linked via a ring carbon atom and containing one to three heteroatoms independently selected from nitrogen, oxygen and sulphur); and a 9- or 10-membered bicyclic heterocyclic moiety (linked via a ring carbon atom and containing one or two nitrogen heteroatoms and optionally containing a further one or two heteroatoms selected from nitrogen, oxygen and sulphur);

and one or both of Q_1 and Q_2 bears on any available carbon atom one substituent of the formula **(Ia)** and Q_2 may optionally bear on any available carbon atom further substituents of the formula **(Ia)**:



(Ia)

[provided that when present in Q_1 the substituent of formula **(Ia)** is not adjacent to the -NH- link];

wherein:

X is -CH_2-, -O-, -NH-, -NR^y- or -S- [wherein R^y is C_{1-4}alkyl, optionally substituted by one substituent selected from halo, amino, cyano, C_{1-4}alkoxy or hydroxy];

Y^1 is H, C_{1-4}alkyl or as defined for Z;

Y^2 is H or C_{1-4}alkyl;

Z is R^aO-, R^bR^cN-, R^dS-, $R^eR^fNNR^g$-, a nitrogen linked heteroaryl or a nitrogen linked heterocycle [wherein said heterocycle is optionally substituted on a ring carbon or a ring nitrogen by C_{1-4}alkyl or C_{1-4}alkanoyl] wherein R^a, R^b, R^c, R^d, R^e, R^f and R^g are independently selected from hydrogen, C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl, and wherein said C_{1-4}alkyl and C_{2-4}alkenyl are optionally substituted by one or more phenyl ;

n is 1, 2 or 3;

m is 1, 2 or 3;

and Q_1 may optionally bear on any available carbon atom up to four substituents independently selected from halo, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N',N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl;

and also independently, or where appropriate in addition to, the above substituents, Q_1 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, benzimidazol-2-yl, phenoxy and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl, benzoyl, phenoxy, 5- or

6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear up to five substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy;

and Q_2 may optionally bear on any available carbon atom up to four substituents independently selected from halo, hydroxy, thio, nitro, carboxy, cyano, C_{2-4}alkenyl [optionally substituted by up to three halo substituents, or by one trifluoromethyl substituent], C_{2-4}alkynyl, C_{1-5}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, amino-C_{1-3}alkyl, C_{1-4}alkylamino-C_{1-3}alkyl, di-(C_{1-4}alkyl)amino-C_{1-3}alkyl, cyano-C_{1-4}alkyl, C_{2-4}alkanoyloxy-C_{1-4}-alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, carboxy-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl-C_{1-4}alkyl, carbamoyl-C_{1-4}alkyl, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkyl, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkyl, pyrrolidin-1-yl-C_{1-3}alkyl, piperidino-C_{1-3}alkyl, piperazin-1-yl-C_{1-3}alkyl, morpholino-C_{1-3}alkyl, thiomorpholino-C_{1-3}alkyl, imidazo-1-yl-C_{1-3}alkyl, piperazin-1-yl, morpholino, thiomorpholino, C_{1-4}alkoxy, cyano-C_{1-4}alkoxy, carbamoyl-C_{1-4}alkoxy, *N*-C_{1-4}alkylcarbamoyl-C_{1-4}alkoxy, *N*,*N*-di-(C_{1-4}alkyl)-carbamoyl-C_{1-4}alkoxy, 2-aminoethoxy, 2-C_{1-4}alkylaminoethoxy, 2-di-(C_{1-4}alkyl)aminoethoxy, C_{1-4}alkoxycarbonyl-C_{1-4}alkoxy, halo-C_{1-4}alkoxy, 2-hydroxyethoxy, C_{2-4}alkanoyloxy-C_{2-4}alkoxy, 2-C_{1-4}alkoxyethoxy, carboxy-C_{1-4}alkoxy, 2-pyrrolidin-1-yl-ethoxy, 2-piperidino-ethoxy, 2-piperazin-1-yl-ethoxy, 2-morpholino-ethoxy, 2-thiomorpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{3-5}alkenyloxy, C_{3-5}alkynyloxy, C_{1-4}alkylthio, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, hydroxyC_{2-4}alkylthio, hydroxyC_{2-4}alkylsulphinyl, hydroxyC_{2-4}alkylsulphonyl, ureido, *N'*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)ureido, *N'*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, *N'*,*N'*-di-(C_{1-4}alkyl)-*N*-(C_{1-4}alkyl)ureido, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N*,*N*-di-(C_{1-4}alkyl)carbamoyl, amino, C_{1-4}alkylamino, di-(C_{1-4}alkyl)amino, C_{2-4}alkanoylamino, sulphamoyl, *N*-(C_{1-4}alkyl)sulphamoyl, *N*,*N*-di-(C_{1-4}alkyl)sulphamoyl,

and also independently, or where appropriate in addition to, the above optional substituents, Q_2 may optionally bear on any available carbon atom up to two further substituents independently selected from C_{3-8}cycloalkyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenylthio, phenyl, naphthyl, benzoyl, phenoxy, benzimidazol-2-yl, and a 5- or 6-membered aromatic heterocycle (linked via a ring carbon atom and containing one to three heteroatoms independently selected from oxygen, sulphur and nitrogen); wherein said naphthyl, phenyl,

benzoyl, phenoxy, 5- or 6-membered aromatic heterocyclic substituents and the phenyl group in said phenyl-C_{1-4}alkyl, phenylthio and phenyl-C_{1-4}alkoxy substituents may optionally bear one or two substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

2. A pyrimidine derivative according to claim 1 wherein R^1 is hydrogen, methyl, $-CH_2CH_2CH_2CF_3$, $-CH_2CH=CHBr$, $-CH_2CH=CHPh$; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

3. A pyrimidine derivative according to claims 1 or 2 wherein R^x is selected from fluoro, chloro, bromo, nitro, amino, cyano, carboxy, methyl, methoxy, ethoxy, ethoxymethyl, vinyl, allyloxymethyl, hydroxymethyl, 2-hydroxyethoxymethyl, 4-hydroxybutoxymethyl, dimethylaminomethyl, diethylaminomethyl, ureidomethyl, formamidomethyl, methylaminomethyl, isopropylaminocarbonyl, phenyl, benzyl, phenethyl, benzoylamino, 4-phenylbutyryl, 2-phenylvinyl (optionally substituted by fluoro), benzyloxymethyl, cyclohexyloxymethyl, 3-cyclopentylpropionyl, morpholino, furyl, imidazolylmethyl, isoxazolyloxymethyl (optionally substituted by methyl), quinolinylaminomethyl, benzothienylaminomethyl, pyrazolylaminomethyl, isoxazolylaminomethyl, thiazolylthiomethyl and tetrazolylthiomethyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

4. A pyrimidine derivative according to any one of claims 1 to 3 wherein Q_1 and Q_2 are selected from phenyl, pyridyl, indanyl, indazolyl, indolyl, quinolyl, pyrazolyl or thiazolyl; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

5. A pyrimidine derivative according to any one of claims 1 to 4 wherein the substituent of formula (Ia) is 3-amino-2-hydroxypropoxy, 3-methylamino-2-hydroxypropoxy, 3-dimethylaminopropoxy, 3-dimethylamino-2-hydroxypropoxy, 3-ethylamino-2-hydroxypropoxy, 3-diethylaminopropoxy, 3-isopropylaminopropoxy, 3-isopropylamino-2-hydroxypropoxy, 3-isopropylamino-2-hydroxy-2-methylpropoxy, 3-isobutylamino-2-hydroxypropoxy, 3-*t*-butylamino-2-hydroxypropoxy,

3-ethoxy-2-hydroxypropoxy, 3-(*N*-isopropyl-*N*-benzylamino)-2-hydroxypropoxy, 3-(*N*-allyl-*N*-methylamino)-2-hydroxypropoxy, 3-(4-methylpiperazin-1-yl)propoxy, 3-(4-methylpiperazin-1-yl)-2-hydroxypropoxy, 3-(4-acetylpiperazin-1-yl)-2-hydroxypropoxy, 3-morpholinopropoxy, 3-morpholino-2-hydroxypropoxy, 3-cyclopentylamino-2-hydroxypropoxy, 3-pyrrolidin-1-yl-2-hydroxypropoxy, 3-imidazol-1-ylpropoxy, 3-(*N',N'*-dimethylhydrazino)-2-hydroxypropoxy, 3-*N',N'*-dimethylaminopropylamino, 3-*N',N'*-dimethylamino-2,2-dimethylpropylamino, 3-*N',N'*-dimethylamino-2-hydroxy-*N*-methylpropylamino, 3-*N'*-isopropylaminopropylamino or 3-imidazol-1-ylpropylamino; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

6. A pyrimidine derivative according to any one of claims 1 to 5 wherein Q_2 is optionally substituted by halo, hydroxy, cyano, C_{1-6}alkyl, hydroxy-C_{1-3}alkyl, fluoro-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-3}alkyl, morpholino, C_{1-4}alkoxy, 2-morpholino-ethoxy, 2-imidazo-1-yl-ethoxy, C_{1-4}alkylthio, carbamoyl, amino, C_{2-4}alkanoylamino, sulphamoyl, phenyl-C_{1-4}alkyl, phenyl-C_{1-4}alkoxy, phenyl and phenoxy; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

7. A pyrimidine derivative according to any one of claims 1 to 6 wherein Q_1 is optionally substituted by halo; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

8. A pyrimidine derivative according to any one of claims 1 to 7 wherein the substituent of formula **(Ia)** is on Q_1; or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

9. A pyrimidine derivative according to any one of claims 1 to 8 which is:
5-bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-anilinopyrimidine;
5-bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-(pyrid-2-ylamino)pyrimidine;
5-bromo-2-{4-[2-hydroxy-3-(isopropylamino)propoxy]anilino}-4-(6-methylpyrid-2-ylamino)pyrimidine;

5-bromo-2-{4-[3-(isopropylamino)propoxy]anilino}-4-anilinopyrimidine;

5-bromo-2-{4-[3-(imidazol-1-yl)propoxy]anilino}-4-(6-methylpyrid-2-ylamino)pyrimidine;

or

4-anilino-5-bromo-2-{4-[2-hydroxy-2-methyl-3-(isopropylamino)propoxy]anilino}pyrimidine

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

10. A pyrimidine derivative according to any one of claims 1 to 8 which is:

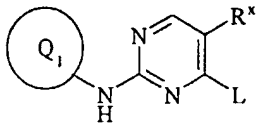
5-bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-(4-chloroanilino) pyrimidine; or

5-bromo-2-{4-[2-hydroxy-3-(*N,N*-dimethylamino)propoxy]anilino}-4-[*N*-(4,4,4-trifluorobutyl)anilino]pyrimidine;

or pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

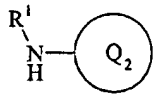
11. A process for preparing a pyrimidine derivative of the formula **(I)** which comprises of:-

a) reacting a pyrimidine of formula **(II)**:



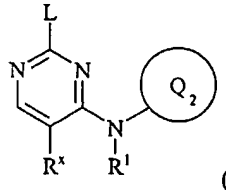
(II)

wherein L is a displaceable group, with a compound of formula **(III)**:



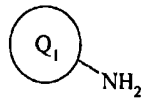
(III)

b) reaction of a pyrimidine of formula **(IV)**:



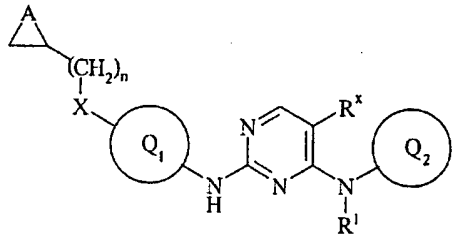
(IV)

wherein L is a displaceable group, with a compound of formula (V):



(V)

c) for compounds of formula (I) where n is 1, 2 or 3, m = 1, Y^2 is H and Y^1 is OH, NH_2 or SH by reaction of a 3-membered heteroalkyl ring of formula (VI):



(VI)

wherein A is O, S or NH; with a nucleophile of formula (VII):

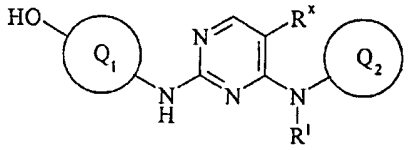
Z-D

(VII)

wherein D is H or a suitable counter-ion;

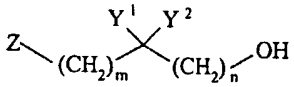
d) for compounds of formula (I) where X is oxygen:

by reaction of an alcohol of formula (VIII):



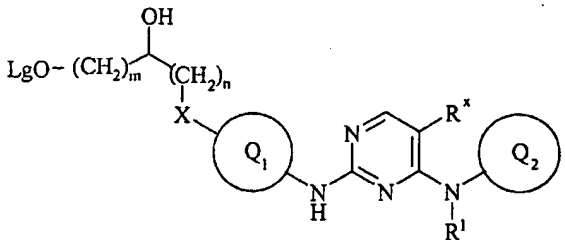
(VIII)

with an alcohol of formula (IX):



(IX)

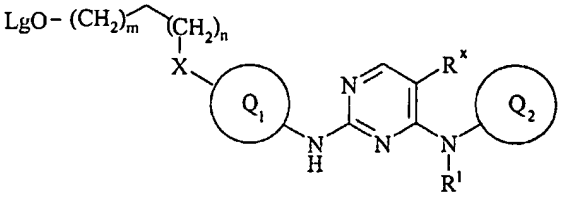
e) for compounds of formula (I) wherein X is $-CH_2-$, -O-, -NH- or -S-, Y^1 is OH, Y^2 is H and m is 2 or 3; reaction of a compound of formula (X):



(X)

wherein LgO is a leaving group; with a nucleophile of formula (VII);

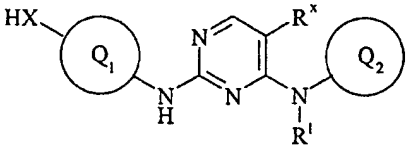
f) for compounds of formula (I) wherein X is $-CH_2-$, -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XI):



(XI)

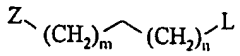
wherein LgO is a leaving group; with a nucleophile of formula (VII);

g) for compounds of formula (I) wherein X is -O-, -NH- or -S-; Y^1 and Y^2 are H; n is 1, 2 or 3 and m is 1, 2 or 3; reaction of a compound of formula (XII):



(XII)

with a compound of formula (XIII)



(XIII)

wherein L is a displaceable group;

h) for compounds of formula (I) in which Z is HS-, by conversion of a thioacetate group in a corresponding compound;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

12. A method for producing an anti-cancer effect in a warm blooded animal which comprises administering to said animal an effective amount of a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt, or *in vivo* hydrolysable ester thereof.

13. The use of a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically-acceptable salt, or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the production of an anti-cancer effect in a warm blooded animal.

14. A pharmaceutical composition which comprises a pyrimidine derivative of the formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, and a pharmaceutically-acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04325

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/48 C07D401/12 C07D239/50 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 95, no. 11, 1981 Columbus, Ohio, US; abstract no. 97712f, GHOSH,D.: "2,4-BIS(ARYLAMINO)-6-METHYLPYRIMIDINES AS ANTIMICROBIAL AGENTS" page 648; XP002109184 abstract & J.INDIAN CHEM. SOC., vol. 58, no. 5, 1981, pages 512-13, INDIA	1,14
A	WO 91 18887 A (SMITH KLINE) 12 December 1991 (1991-12-12) page 38; claims	1,14

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2000	14/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/04325

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 50250 A (JANSSEN) 7 October 1999 (1999-10-07) the whole document	1,14

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 99/04325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9118887 A	12-12-1991	AU 7971691 A	31-12-1991
WO 9950250 A	07-10-1999	AU 3599699 A	18-10-1999
		EP 0945443 A	29-09-1999
		EP 0945442 A	29-09-1999